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The natural history of childhood-onset nonallergic rhinitis; a long-term follow-up study

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Abstract

Background: Non-allergic rhinitis (NAR) is characterized by symptoms of nasal inflammation without allergic sensitization. The long-term outcome of NAR in children is poorly defined.

Objective: To determine the natural history of childhood-onset NAR and the development of allergic rhinitis (AR) in these children.

Methods: NAR patients who were followed for more than 10 years were evaluated at 3-5 years (E2) and 9-12 years (E3) after the first evaluation (E1). Nasal symptoms, disease severity, comorbidities, medication used, and aeroallergen sensitization were assessed.

Results: Eighty-two NAR patients (58.5% male) completed all 3 evaluations. The age at onset was 2.0 (range 2.0-4.0) years. The follow-up period was 13.6 (range 12.3-14.3) years. At E2, 37.8% of patients developed AR. At E3, the patients were classified into four groups based on results of skin prick tests in E2 and E3 (group I: NAR→NAR→NAR, 39.0%, group II: NAR→NAR→AR, 23.2%, group III: NAR→AR→NAR, 12.2% and group IV: NAR→AR→AR, 25.6%). The most common aeroallergen sensitization was house dust mite. The family history of atopy, asthma and allergic rhinitis were higher in group III and IV than other groups ($p < 0.05$). The atopic dermatitis, obstructive sleep apnea and adenotonsillar hypertrophy at E1 and E2 were predominantly found in group IV ($p < 0.05$). At E2, group III and IV patients had higher proportion of exposure to house dust, animal dander and smoking compared to other groups ($p < 0.05$). The overall remission rate was 14.6%.

Conclusion: Children with NAR should be reevaluated periodically to determine aeroallergen sensitization for the appropriate diagnosis and management.

Key words: allergic rhinitis, childhood-onset nonallergic rhinitis, children, natural history, nonallergic rhinitis, sensitization

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Introduction

Rhinitis is an inflammatory condition of the nasal mucosa that causes rhinorrhea, sneezing, nasal itching and obstruction.[1-3] These symptoms occur on two or more consecutive days for more than one hour on most days.[4,5] Based on the duration of nasal symptoms, rhinitis can be divided into acute rhinitis (duration less than 12 weeks), and chronic rhinitis (presenting at least 1 hour/day and at least 12 weeks/year).[6] Chronic rhinitis can significantly affect quality of life, school performance, sleep quality, and emotional health.[1-3,7]

Chronic rhinitis can be classified as allergic rhinitis (AR) and nonallergic rhinitis (NAR). AR is the most common form of non-infectious rhinitis with IgE-mediated inflammation of the nasal mucosa triggered by aeroallergens such as house dust mites, animal dander, or pollens.[3-5] The diagnosis of AR is based on the presence of chronic rhinitis symptoms and evidence of IgE sensitization by skin prick tests (SPT) or specific IgE (sIgE) to an aeroallergen.[4,8] NAR is defined as chronic rhinitis with at least two nasal symptoms such as nasal obstruction, rhinorrhea, sneezing, and/or nasal itching, without clinical evidence of endonasal infection and without aeroallergen sensitization.[4,6] NAR is diagnosed by nasal symptoms similar to AR with negative SPT or sIgE to aeroallergen.[2-6,8,9] The triggering factors for NAR include changes in temperature or weather, tobacco smoke, exhausted fumes, and irritants such as strong odors.[10]

In adults, AR is more common and affects 20-30% of the population, while the prevalence of NAR is estimated to be 10-15%.[4,11] NAR generally presents predominantly with adult onset and a female:male ratio of 2-3:1.[12] In contrast, the prevalence of NAR in children is not well established. In a Swedish birth cohort study, the prevalence of NAR was 8.1% and 6.3% at 4 years and 8 years, respectively.[13] The prevalence ratio of NAR and AR in children is estimated to be at least 1:3-4, similar to adults.[14-17]

Changing pattern of aeroallergen sensitization upon follow-up can be found in patients with NAR. Rondón et al. reported that 24% of adult patients with NAR developed aeroallergen sensitization within 3-7 years of follow-up.[18] In pediatrics, 5.6-40% of NAR children developed aeroallergen sensitization after 3 to 5 years of follow-up.[13,19] However, long-term follow-up of NAR in children has not been well studied. Therefore, our objective was to determine the extended natural history of NAR and the continuous development of AR in pediatric population.

Methods

Study design and subjects

This study was conducted at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. It was approved by the Institutional Review Board, Siriraj Hospital (approval no. 333/2562, COA no. Si 239/2019). Informed consent was obtained prior to the study. We recruited patients who were diagnosed with NAR and were followed by pediatric allergists in the pediatric allergy clinic at Siriraj hospital for more than 10 years. Demographic data were obtained from the medical records and interview. Patients were invited for reevaluation visits. The second and third evaluations were completed at 3-5 years and 9-12 years after the first evaluation. Current symptoms, comorbidities, and medications for rhinitis were obtained at the third evaluation. SPT to the same panel of aeroallergens as it was performed in the first evaluation, was repeated at the second and third evaluations. Patients who did not complete the second and third evaluations were excluded.

AR was clinically defined by chronic rhinitis symptoms that included rhinorrhea, nasal obstruction, nasal itching, and sneezing after exposure to allergens with positive SPT to aeroallergens.[4,5,8] NAR was defined by chronic rhinitis symptoms, with at least two symptoms (nasal obstruction, anterior rhinorrhea/postnasal drip, sneezing, or nasal/ocular itching) and without clinical evidence of nasal infection and with negative SPT to aeroallergens.[2-6,8,9,20,21]

The severity and persistence of rhinitis symptoms were classified as mild, moderate or severe, and intermittent or persistent according to the 2019 Allergic Rhinitis and Its Impact on Asthma (ARIA).[22] Mild rhinitis was defined as symptoms of rhinitis that did not disrupt activities of daily life, including sleep, while moderate to severe rhinitis affected these activities. Intermittent rhinitis was defined as rhinitis symptoms less than four days a week or less than four consecutive weeks, while persistent rhinitis was defined as rhinitis symptoms lasting more than four days a week and more than four consecutive weeks.[5,22] Remission of rhinitis was defined as the absence of rhinitis symptoms without using any medication to control symptoms for at least one year.[23]

Comorbidities including asthma, adenotonsillar hypertrophy, obstructive sleep apnea (OSA), chronic rhinosinusitis, eye symptoms, atopic dermatitis and food allergy were collected. Environmental factors (cigarette smoke exposure and pets in house) and aggravating factors (exposure to house dust, animal dander, irritant, pollen, temperature, and seasonal changes) were obtained.

Skin prick test

Skin prick test was performed to detect the most prevalent aeroallergen sensitization including house dust mites (*Dermatophagoides pteronyssinus*, *Dp* and *Dermatophagoides farinae*, *Df*), American and German cockroaches, cat and dog dander, Acacia, Careless weeds, grass pollens (Bermuda and Johnson), and molds (*Alternaria* spp., *Cladosporium* spp., *Penicillium* spp., *Aspergillus* spp., and *Curvularia* spp.). Commercial allergens from ALK-Abello, Port Washington, NY, were used. Histamine (10 mg/mL) and glycerine were used as positive and negative controls, respectively. The SPT was considered positive if there was a mean wheal diameter of 3 mm larger than the negative control for at least one aeroallergen. Patients were asked to discontinue antihistamines for at least seven days prior to skin tests.

Total nasal symptom score (TNSS) and medication score

At the third evaluation, the total nasal symptom score (TNSS) in the past four weeks were assessed using the sum of four individual symptoms scores for rhinorrhea, nasal congestion, nasal itching, and sneezing, with a scale of 0 = no symptom, 1 = mild, 2 = moderate, or 3 = severe symptom based on the disturbance of daily activities (possible score of 0-12).[24]

The daily medications were calculated as the medication score. The scores for the different medications were designated as follows: 0 = no medication, 1 = patient took oral or ocular antihistamine, 2 = patient took intranasal or inhaled corticosteroids or leukotriene receptor antagonist (LTRA) or decongestant, and 3 = patient took oral corticosteroid.[25,26] The TNSS and medication score were combined into a total combination score.[27]

Statistical analysis

The demographic data, comorbidities, and triggering factors were analyzed using descriptive analysis (frequencies, percentages, median, and range). The chi-squared test was used to compare data between persistent NAR and patients who developed AR. Quantitative data (age of onset, medication scores, TNSS and combination score) were analyzed using the Mann-Whitney U test. The significance level was set at the *p*-value ≤ 0.05 or when the 95% confidence intervals (CI) of the odds ratio did not contain the value of 1.

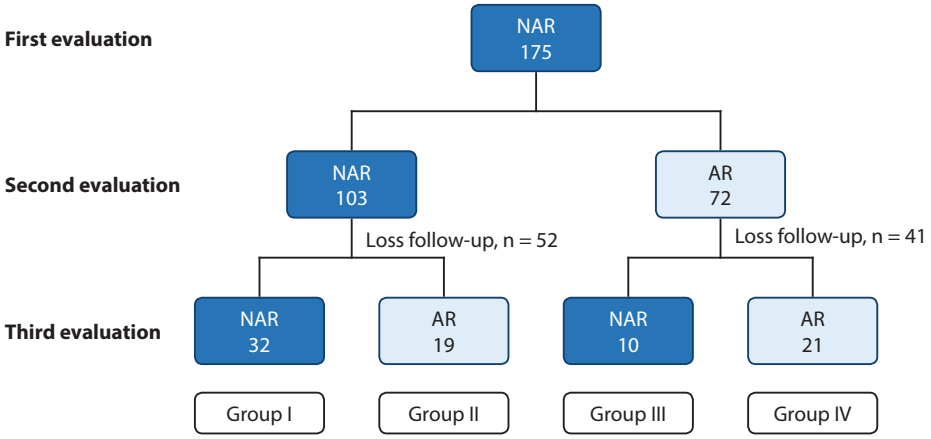
Results

Demographic data and group allocation

Eighty-two of the 175 NAR patients who had completed three evaluation visits were recruited in this study (**Figure 1**). At the third evaluation, 52 patients in the NAR and 41 patients in the AR group were loss to follow-up. However, there was no significant difference in sex, age of onset, family history of atopy and baseline severity of rhinitis symptoms between follow-up and non-follow-up NAR and AR patients in the second evaluation (data not shown).

The patients were classified into four groups according to the result of SPT to aeroallergens at each evaluation. Group I (n = 32, 39.0%) were patients diagnosed with NAR in the second and third evaluations. Group II (n = 19, 23.2%) were patients diagnosed with NAR in the second evaluation but developed AR in the third evaluation. Group III (n = 10, 12.2%) were patients diagnosed with AR in the second evaluation but turned to NAR in the third evaluation. Group IV (n = 21, 25.6%) were patients diagnosed with AR in the second and third evaluations (**Figure 1**).

At the second evaluation, the most common sensitized aeroallergen in patients who developed AR was house dust mites 64.5% (*Dp* 61.3%, *Df* 54.8%), followed by cockroaches 38.7% (American cockroach 35.5%, German cockroach 25.8%), Bermuda 29.0%, Johnson 12.9%, cat 12.9%, molds 9.7%, acacia 9.7%, and careless weed 6.5%. At the third evaluation, AR patients were sensitized to house dust mite 87.5% (*Dp* 85.0%, *Df* 72.5%), cockroach 40% (American cockroach 30.0%, German cockroach 30.0%), cat 27.5%, Bermuda 22.5%, molds 12.5%, dog 10.0%, Johnson 10%, acacia 7.5% and careless weed 7.5%.



Groups of the patients (n, %)	First evaluation	Second evaluation	Third evaluation
Group I (32, 39%)	NAR	NAR	NAR
Group II (19, 23.2%)	NAR	NAR	AR
Group III (10, 12.2%)	NAR	AR	NAR
Group IV (21, 25.6%)	NAR	AR	AR

Figure 1. Participants' data availability at the 1st, 2nd, and 3rd evaluations. Skin prick test to aeroallergens was conducted at each evaluation.

The demographic data are shown in **Table 1**. Forty-eight patients (58.5%) were males. The median follow-up period was 13.7 (range 12.3-14.3) years. The median age of onset of chronic rhinitis was 2.0 (range 2.0-4.0) years and the mean ± SD age at the third evaluation was 18.7 ± 3.3 years. Among the four groups, group II had a mean age at the third evaluation less than other groups ($p = 0.02$). The family history of atopy, asthma and AR were higher in group III and IV than group I and II ($p < 0.01$, $p = 0.02$ and $p < 0.01$, respectively).

Comorbidities

The comorbidities at all evaluations were shown in **Table 1**. At the first and the second evaluation, atopic dermatitis, OSA and adenotonsillar hypertrophy were predominantly found in group IV ($p \leq 0.05$). Food allergy was predominantly found in group III and IV at both evaluations ($p \leq 0.05$). At the third evaluation, none of the patients reported atopic dermatitis, OSA or adenotonsillar hypertrophy and there was no significantly different of comorbidity among all groups.

Table 1. Demographic data of the patients with NAR who were classified into four groups.

Characterisitcs	Group I (n = 32)	Group II (n = 19)	Group III (n = 10)	Group IV (n = 21)	*p*-value
Sex: male, n (%)	21 (65.6%)	14 (73.7%)	5 (50%)	8 (38.1%)	0.09
Median (range) age of onset (years)	3 (2.0, 5.8)	2 (2.0, 3.5)	3 (2.0, 3.3)	2 (1.0, 3.0)	0.16
Mean age ± SD at the 3rd evaluation (years)	19.7 ± 3.3	16.98 ± 2.6	20.2 ± 3.0	18.7 ± 3.3	**0.02***
Family history, n (%)					
Atopy	10 (31.2%)	3 (15.8%)	8 (80.0%)	17 (81.0%)	**< 0.01***
Asthma	2 (6.2%)	0 (0.0%)	1 (10.0%)	8 (38.1%)	**0.02***
Allergic rhinitis	8 (25.0%)	3 (15.8%)	7 (70.0%)	14 (66.7%)	**< 0.01***
Food allergy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	0.61
Comorbidities at the 1st evaluation, n (%)					
Atopic dermatitis	1 (3.1%)	0 (0.0%)	1 (10.0%)	5 (23.8%)	**0.03***
Obstructive sleep apnea	3 (9.4%)	2 (10.5%)	0 (0.0%)	8 (38.1%)	**0.02***
Adenotonsillar hypertrophy	4 (12.5%)	3 (15.8%)	1 (10.0%)	9 (42.9%)	**0.05***
Allergic conjunctivitis	9 (28.1%)	1 (5.3%)	2 (20%)	1 (4.8%)	0.06
Chronic rhinosinusitis	9 (28.1%)	5 (26.3%)	1 (10%)	5 (23.8%)	0.72
Immunodeficiencies	7 (21.9%)	3 (15.8%)	0 (0.0%)	2 (9.5%)	0.37
Food allergy	0 (0.0%)	0 (0.0%)	2 (20%)	3 (14.3%)	**0.02***
Comorbidities at the 2nd evaluation, n (%)					
Atopic dermatitis	1 (3.1%)	0 (0.0%)	1 (10.0%)	5 (23.8%)	**0.03***
Obstructive sleep apnea	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (14.3%)	**0.05***
Adenotonsillar hypertrophy	0 (0.0%)	1 (5.3%)	0 (0.0%)	4 (19%)	**0.03***
Allergic conjunctivitis	3 (9.4%)	1 (5.3%)	2 (20.0%)	6 (28.6%)	0.15
Chronic rhinosinusitis	1 (3.1%)	1 (5.3%)	0 (0.0%)	3 (14.3%)	0.38
Food allergy	0 (0.0%)	0 (0.0%)	1 (10.0%)	3 (14.3%)	**0.03***
Comorbidities at the 3rd evaluation, n (%)					
Asthma	4 (12.5%)	3 (15.8%)	1 (10.0%)	5 (23.8%)	0.71
Allergic conjunctivitis	2 (6.2%)	1 (5.3%)	1 (10.0%)	2 (9.5%)	1.00
Chronic rhinosinusitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	0.60
Food allergy	0 (0.0%)	0 (0.0%)	1 (10.0%)	2 (9.5%)	0.11

*statistically significant among 4 groups of patients

Environmental and triggering factors

At the first evaluation, the most common triggering factor in all groups was the change in temperature. None of the patients were triggered by pollen. Patients in group III had significantly lower proportion of change in temperature as a triggering factor (p = 0.01). Patients in group III and IV had higher proportion of smoking in the house compared to patients in group I and II (p = 0.02) (**Table 2**).

At the second evaluation, the change in temperature was also the most common triggering factor in all groups. However, patients in group III and IV had significantly lower proportion of change in temperature as a triggering factor compared to patients in group I and II (p < 0.01). House dust and animal dander exposure were dominant triggering factors in group III and IV patients when compared to group I and II patients (p = 0.02 and p = 0.02, respectively). Additionally, patients in group III and IV had higher proportion of smoking in the house compared to patients in group I and II (p = 0.01).

At the third evaluation, none of triggering and environmental factors were different among 4 groups of patients.

Table 2. Environmental and triggering factors at initial, 2nd and 3rd evaluations in all groups.

Parameters	Group I (n = 32)	Group II (n = 19)	Group III (n = 10)	Group IV (n = 21)	*p*-value
At the 1st evaluation					
Triggering factors, n (%)					
House dust	10 (31.2%)	3 (15.8%)	2 (20%)	8 (38.1%)	0.40
Irritants	9 (28.1%)	5 (26.3%)	4 (40%)	6 (28.6%)	0.89
Animal dander	2 (6.2%)	1 (5.3%)	0 (0.0%)	2 (9.5%)	1.00
Temperature change	32 (100.0%)	10 (100.0%)	8 (80.0%)	21 (100.0%)	**0.01***
Environmental factors					
Smoking in the house	9 (28.1%)	6 (31.6%)	7 (70.0%)	13 (61.9%)	**0.02***
Pet in the house	16 (50.0%)	4 (21.1%)	4 (40.0%)	9 (42.9%)	0.24
At the 2nd evaluation					
Triggering factors, n (%)					
House dust	11 (34.4%)	3 (15.8%)	6 (60.0%)	15 (71.4%)	**0.02***
Irritants	10 (31.3%)	4 (21.1%)	6 (60.0%)	7 (33.3%)	0.21
Animal dander	1 (3.1%)	0 (0.0%)	2 (20.0%)	5 (23.8%)	**0.02***
Temperature change	32 (100%)	19 (100%)	8 (80.0%)	17 (81.0%)	**< 0.01***
Environmental factors					
Smoking in the house	9 (28.1%)	5 (26.3%)	6 (60.0%)	14 (66.7%)	**0.01***
Pet in the house	15 (46.9%)	6 (31.6%)	3 (30.0%)	9 (42.9%)	0.64
At the 3rd evaluation					
Triggering factors, n (%)					
House dust	18 (56.3%)	8 (42.1%)	7 (70.0%)	12 (57.1%)	0.52
Irritants	18 (56.3%)	4 (21.1%)	5 (50.0%)	7 (33.3%)	0.07
Animal dander	1 (3.1%)	4 (21.1%)	2 (20.0%)	3 (14.3%)	0.13
Temperature change	17 (53.1%)	10 (52.6%)	4 (40.0%)	7 (33.3%)	0.48
Environmental factors					
Smoking in the house	10 (31.3%)	5 (26.3%)	6 (60.0%)	9 (42.9%)	0.26
Pet in the house	12 (37.5%)	6 (31.6%)	3 (30.0%)	12 (57.1%)	0.31

*statistically significant among 4 groups of patients

Table 3. The nasal symptoms at the initial, 2nd and 3rd evaluations in all groups.

Nasal symptoms	Group I (n = 32)	Group II (n = 19)	Group III (n = 10)	Group IV (n = 21)	*p*-value
At the 1st evaluation					
Nasal congestion	29 (90.6%)	18 (94.7%)	9 (90.0%)	20 (95.2%)	1.00
Nasal itching	9 (28.1%)	3 (15.8%)	3 (30.0%)	7 (33.3%)	0.65
Sneezing	10 (31.3%)	3 (15.8%)	2 (20.0%)	6 (28.6%)	0.62
Rhinorrhea	32 (100%)	19 (100%)	10 (100%)	21 (100%)	-
At the 2nd evaluation					
Nasal congestion	17 (53.1%)	13 (68.4%)	7 (70.0%)	13 (61.9%)	0.66
Nasal itching	3 (9.4%)	4 (21.1%)	5 (50.0%)	12 (57.1%)	**0.001***
Sneezing	13 (40.6%)	7 (36.8%)	4 (40.0%)	16 (76.2%)	**0.04***
Rhinorrhea	25 (78.1%)	16 (84.2%)	8 (80.0%)	19 (90.5%)	0.67
At the 3rd evaluation					
Nasal congestion	19 (59.4%)	12 (63.2%)	5 (50.0%)	11 (52.4%)	0.86
Nasal itching	18 (56.3%)	7 (36.8%)	4 (40.0%)	9 (42.9%)	0.53
Sneezing	19 (59.4%)	11 (57.9%)	4 (40.0%)	12 (57.1%)	0.75
Rhinorrhea	14 (43.8%)	7 (36.8%)	4 (40.0%)	8 (38.1%)	0.96

*statistically significant among 4 groups of patients

The rhinitis score, severity and persistence of rhinitis symptoms and remission at the third evaluation

Comparisons of rhinitis symptoms (nasal congestion, nasal itching, sneezing and rhinorrhea) in each evaluation are shown in **Table 3**. All patients had rhinorrhea at the first evaluation. At the second evaluation, nasal itching was predominantly found in group III and IV ($p < 0.01$) and sneezing was predominantly in group IV ($p = 0.04$) when compared to other groups. On the other hand, all of the patients among 4 groups had no difference of each rhinitis symptom at the first and third evaluations.

The TNSS, medication and combination scores at the third evaluation were not significantly different among all groups (**Figure 2A**). When comparing these scores in patients with NAR (group I and III) or AR (group II and IV) at the third evaluation, the TNSS, medication, and combination were not significantly different (3 (range 0-7) vs 2 (range 0-9), $p = 0.95$, 1 (range 0-5) vs 0 (range 0-6), $p = 0.99$, 4 (range 0-10) vs 5 (range 0-11), $p = 0.71$, respectively).

For the medication use, 42.6% of the patients used intranasal corticosteroid (INS, group I 43.7%, group II 31.6%, group III 40.0% and group IV 52.4%) and 46.3% of the patients used oral antihistamine (group I 53.1%%, group II 36.8%, group III 30.0% and group IV 52.4%). Only 2 and 4 patients took LTRA and ocular antihistamine, respectively. The medication used in chronic rhinitis is not significantly different among the 4 groups. None of the patient used intranasal antihistamine, systemic corticosteroid or long term antibiotic.

Most of the patients with INS treatment took INS regularly (group I: 78.6%, group II: 83.3%, group III 75%, group IV 90.9%, $p = 0.15$). On the other hand, patients with antihistamine treatment took this medication according to the allergic status (group I 24.4%, group II 71.4%, group III 33.3% and group IV 72.7%), but the frequency was not significantly different among the 4 groups ($p = 0.07$).

At the third evaluation, the overall remission rate was 14.6%. The remission rate in group I was 6.2%, group II 10.5%, group III 30% and group IV 23.8%. The trend of the severity and persistence of rhinitis symptoms in each evaluation was shown in **Figure 2B**. Patients who had no symptom were found at the third evaluation but not the first or second evaluation.

At the third evaluation, group III and IV had higher proportion of patients without symptoms compared to group I and II ($p = 0.05$). Patients in group III had either no or mild intermittent rhinitis symptoms. The group II and IV had higher proportion of moderate to severe intermittent severity compared to group I and III ($p = 0.05$).

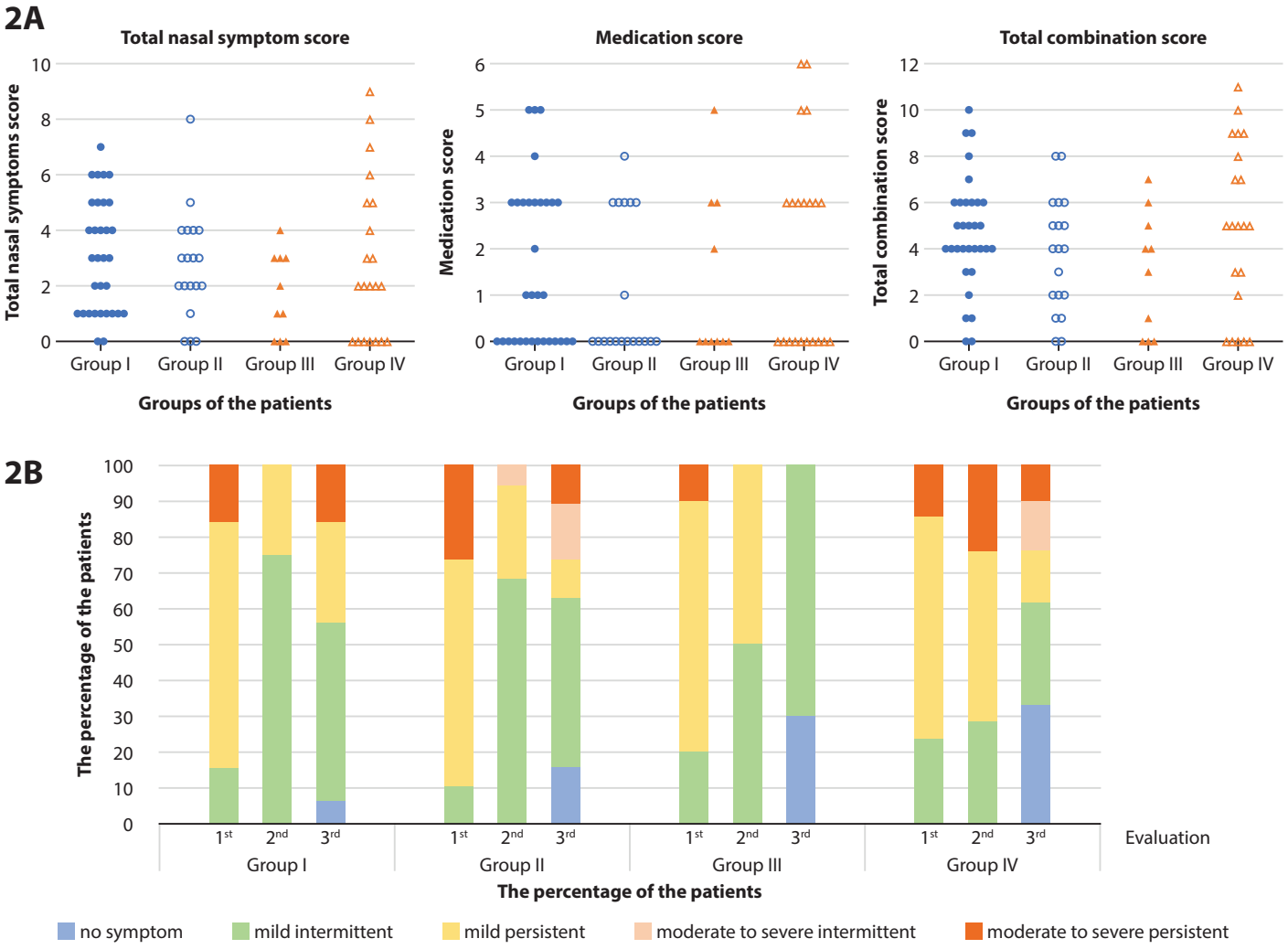


Figure 2. The dot plot of total nasal symptom score, medication score and combination score among 4 groups at the third evaluation (2A) and the trend of severity and persistency of rhinitis symptoms at each evaluation of 4 groups of patients (2B).

Discussion

NAR is a common condition that affects more adults than children.[15] Seventy percent of patients with NAR are diagnosed at more than 20 years of age.[21] In adults, NAR accounts for 17-52% of chronic rhinitis cases, occurs more frequently in females than males (58% vs. 42%, respectively), and the symptoms of rhinitis are more likely to be perennial than seasonal.[20,21] In children, AR was three times more common than NAR and found more often in males than females.[16,28]

Patients with NAR could develop AR upon follow up. In adults, Rondon et al. reported that 24% of NAR developed sensitization to new aeroallergens and were diagnosed with AR after 3-7 years of follow-up.[18] In children, Lee SH, et al. followed seven-year-old children with NAR for two years and found that 26% developed AR.[29] However, a Swedish birth cohort analyzed sensitization data and found that only 5.6% of children with NAR at age four had developed AR four years later.[13] Our previous study in Thailand found that 41% of children with NAR developed sensitization to aeroallergens and were diagnosed with AR after 3-5 years.[19]

This current study followed children with NAR for more than 10 years in an allergic clinic at a tertiary hospital. Thirty-nine percent of the NAR patients (group I) were still not sensitized to aeroallergens during the second and third follow-up evaluations, while 23% (group II) developed aeroallergen sensitization later at the third evaluation. Interestingly, 12% of NAR patients (group III) were sensitized to aeroallergens at the second evaluation but became non-sensitized at the third evaluation. Twenty-six percent of the NAR patients (group IV) developed aeroallergen sensitization at the second evaluation and remained sensitized at the third evaluation (**Figure 1**). **Figure 3** demonstrates the significant factors which influence the natural history of NAR patients.

Our findings were supported by Shin JH et al. who followed adult patients with rhinitis in Korea for 32 months and re-evaluated aeroallergen sensitization at 2 time-points. They reported that 56.5% of rhinitis patients revealed changes in allergen sensitization patterns in which 62.8%

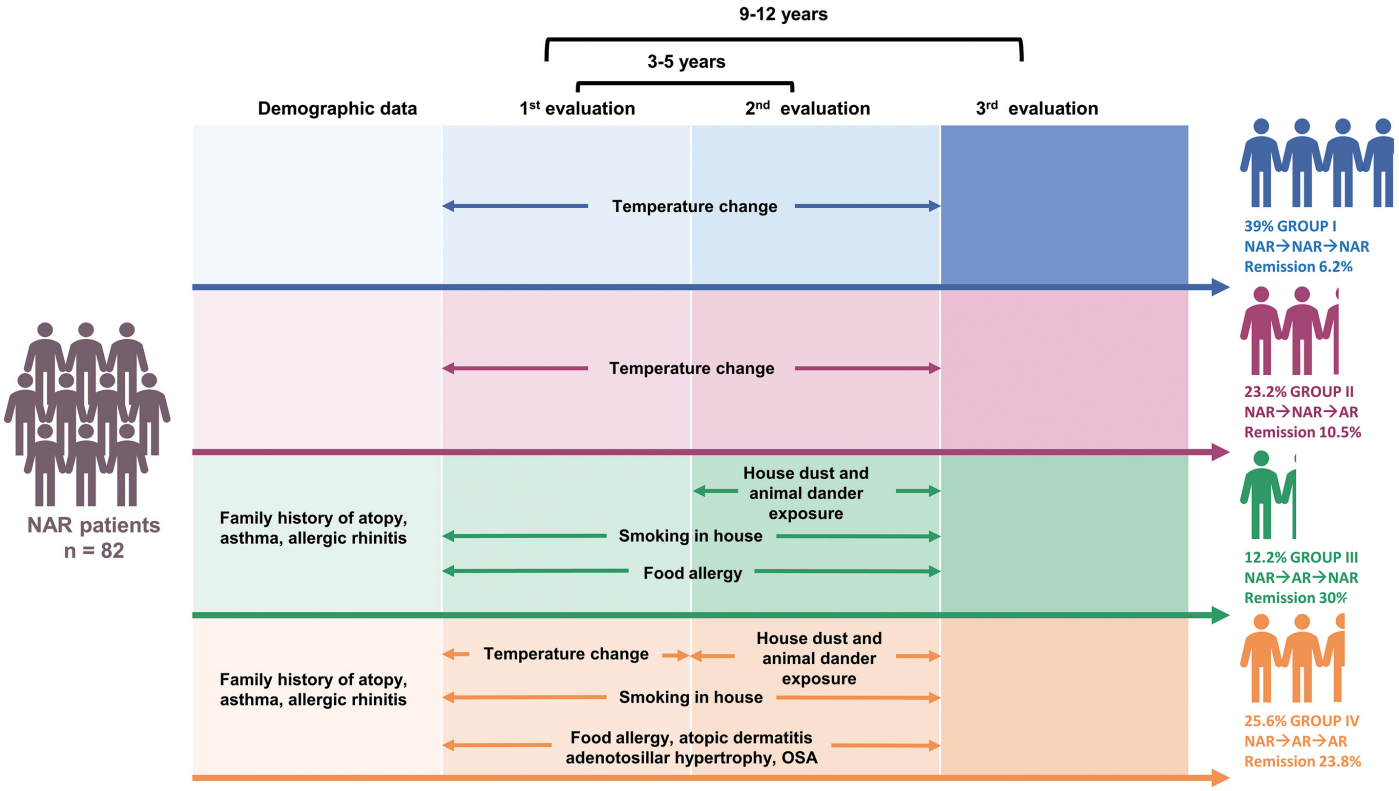


Figure 3. The significant factors at all evaluations which influence the natural history of NAR patients.

developed new sensitization and 66.7% turned to desensitization.[30] Among those who developed new sensitization, 30.6% developed allergen sensitization after lacking sensitization on the first test and 67.3% were sensitized to additional allergens. Among those who turned desensitization, 67.3% became desensitized to one or more allergens (but not all allergens) on the second test, and 32.7% became negative sensitization on the second test.[30] In our study, we also found that 37.8% of NAR patients developed new sensitization at the second evaluation (group III and IV) and 23.2% developed new sensitization at the third evaluation (group II). Interestingly, 12.2% of AR patients turned desensitization at the third evaluation (group III).

Previous studies identified that family history of atopy was a significant predictor for the development of AR.[19,31] Our study found that family history of atopy, asthma and AR were predominantly found in group III and IV patients who developed AR at the second evaluation. This finding might suggest the important role of genetic factor in developing AR in school-age children (**Table 1 and Figure 3**).

In patients who were previously diagnosed with NAR, the most common comorbidities in patients who developed AR later were asthma, atopic dermatitis and food allergy.[16,19,28] In contrast, sinusitis was found to be more common in NAR patients who did not developed AR.[16] Data on OSA have been inconsistent. Vichayanond, et al. found that NAR patients who did not develop AR have more OSA than AR patients.[16] However, Veskitkul, et al. showed that OSA can be found more often in patients with NAR who further developed AR than patients who did not developed AR.[19] Our study found that NAR patients who developed AR at the second and third evaluation (group IV) tended to have more symptoms of atopic dermatitis, OSA, and adenotonsillar hypertrophy and food allergy than other groups at the first and second evaluation. However, there was no significant difference among the 4 groups in the third evaluation as these comorbidities might outgrow at the middle to late adolescent period (**Table 1 and Figure 3**).

In this study, the most common sensitization in patients who developed AR in the second and third evaluations was house dust mites, which was consistent with other reports.[16,19,28] House dust, animal dander and pollen have been reported to trigger symptoms more frequently in NAR patients who developed AR, while temperature change was a more frequent trigger for NAR patients who did not develop AR.[19] Our study observed that temperature change was the most frequent triggering factor in all groups at the first and second evaluations. For the environmental factors, previous studies reported the synergistic effect of family history of atopy and smoke exposure, on increasing the risk of allergic sensitization and allergic diseases including AR.[32,33] In our study, smoking in the house was predominated in group III and IV patients at the first and second evaluation. These two groups also had a strong family history of atopy (**Table 1**). However, the environmental and triggering factors were not different among all groups at the third evaluation (**Table 2**).

The characteristics of NAR in adults and children are different. Adults with NAR tend to have more persistent symptoms than AR patients, but the severity of symptoms is similar.[34] Furthermore, the study by Rondon et al. showed that the persistence and severity of current NAR and developed AR patients were comparable with adult NAR patients.[18] In children, NAR has a wide variety of clinical characteristics and the data on the severity of rhinitis symptoms between NAR and AR groups are discordant. Chiang et al. found that preschool children with AR had more moderate to severe symptoms of nasal itching, sneezing, nasal congestion, and nasal discharge than children with NAR.[28] However, Vichyanond et al. found that there was no difference in the severity of rhinitis between patients with NAR and AR.[16] Veskitkul et al. showed that NAR patients who developed AR experienced more persistent, moderate to severe nasal and eye symptoms than NAR patients who did not develop AR.[19] Our study found that nasal itching was frequently reported in patients who developed AR at the second evaluation (group III and IV) and sneezing was frequently reported in patients who developed AR at both the second and third evaluations (group IV, **Table 3**). However, at the third evaluations, no significant difference was found in total nasal symptom, medication, or combination scores among the 4 groups (**Figure 2A**) and group III and IV had higher proportion of patients without symptoms compared to group I and II (**Figure 2B**).

The main medications used to treat AR and NAR are INS, topical antihistamine sprays, combination therapy with INS and topical antihistamine and as needed oral antihistamine.[22,35] We also found that INS were most used in AR and NAR patients. Group II and IV patients who were diagnosed AR in third evaluation also use daily oral antihistamine because most AR patients in Thailand are perennial AR with house dust mite sensitization.[36]

The remission rate of NAR varies among studies. Westman M et al. revealed that 73% of NAR children experienced remission during a 4-year follow-up.[13] Lee SH et al. showed that 37% of NAR children reported no chronic rhinitis symptoms after two years.[29] Our study found that clinical remission of NAR was 14.6% after more than 10 years of follow-up and there was no difference among all groups. The discrepancy between remission rate of NAR in each study may be from the duration of follow-up and the definition of remission. The two previous studies defined remission as the absence of symptoms of rhinitis symptoms at the follow-up time point but they did not mention about any medication use.[13,29] On the contrary, we defined remission as the absence of rhinitis symptoms and the absence of medication use to control symptoms for at least one year.

To our knowledge, this is the first study to report the characteristics of patients with NAR that went on to develop AR with a follow-up period of more than 10 years. This study may have some limitations. First, the small sample size was due to an expanded time of follow-up in a specific population group and some patients were loss to be contacted. However, the demographic data between the follow-up and the non-follow-up groups were not different. Second, the definition of NAR in this study might consist of both true NAR and local allergic rhinitis (LAR).[37] LAR is chronic rhinitis without evidence of aeroallergen sensitization by SPT or sIgE, but there is a localized IgE-mediated nasal allergic response that was confirmed by a positive nasal allergen provocation test (NAPT).[4,37,38] A systematic review of LAR in adults demonstrated that the proportion of detectable nasal-sIgE in nasal secretions in patients with NAR was 10.2% (7.4-13.4), while the prevalence of LAR in children was far less than in adults.[37,39] The previous study by our group found only 3.7% of children with NAR had a positive NAPT to *Dp*.[40] Due to the complexity of NAPT and the inability to test more than one allergen at once, it is not a practical test to perform routinely.[41] We did not perform NAPT in our participants, so LAR was not was not identified in the group of NAR patients.

Conclusion

Long term follow-up of NAR in children demonstrated that 39% of them had the same diagnosis. The diagnosis was changed to AR at the second or third evaluations in 61% of the patients. Therefore, periodic re-evaluation of aeroallergen sensitization is required to ensure a correct diagnosis. Appropriate management, such as allergen avoidance recommendation and specific treatments, including allergen immunotherapy, can be offered to patients who develop AR.

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