Allergic rhinitis and immunoglobulin deficiency in preschool children with frequent upper respiratory illness

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Summary

Background: **Frequent upper respiratory illness (URI) is a common problem in preschool children. Allergic rhinitis and immunoglobulin (Ig) deficiency are usually suspected as underlying etiologies.**

Objective: **To determine the prevalence of allergic rhinitis and Ig and IgG subclass deficiency in preschool children with frequent URI.**

Methods: **Two thousand eight hundred and seventy-six questionnaires were distributed to the parents of children aged 3-6 years in 24 kindergartens. Firstly, they determined the frequency of URI in the previous year and secondly the prevalence of rhinitis according to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. The skin prick test (SPT) was performed and serum Ig and IgG subclasses were measured in children with frequent URI (≥10 episodes per year). Allergic rhinitis was diagnosed when the child had had rhinitis in the previous 12 months and positive SPT for at least 1 aeroallergen.**

Results: **Two thousand three hundred and one questionnaires (80.01 %) were returned. Ninety-four out of 219 children with frequent URI participated in the study. The prevalence of allergic rhinitis in the participants was 42.55%. Exclusive breastfeeding for at least 6 months had a protective effect, while paternal history of rhinitis was a risk factor. All participants had normal serum IgG, IgA, IgM and IgG subclass levels for age.**

Conclusion: **The prevalence of allergic rhinitis in preschool children with frequent URI in our study was 42.55%. Allergic rhinitis should be considered if they have a family history of allergic rhinitis. Immunoglobulin deficiency was not found in our study.** ***(Asian Pac J Allergy Immunol 2011;29:73-7)***

Key words: *Upper respiratory illness, Preschool children, Prevalence, Allergic rhinitis, Immunoglobulin deficiency*

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Introduction

Frequent upper respiratory illness (URI) is a common problem in preschool children, who frequently need medical attention[1, 2]. They usually present with recurrent or chronic nasal symptoms, i.e. nasal blockage, rhinorrhea, and sneezing. The etiologies can be structural defects, infectious rhinitis, allergic rhinitis, immunodeficiency diseases, or others (non-allergic noninfectious rhinitis)[3, 4]. Consequently, allergists are often consulted about the possibility of allergic rhinitis (AR) or immunoglobulin (Ig) deficiency as a cause. While the former is common and very troublesome[5, 6], the latter is rare but causes high morbidity and mortality if the patient does not receive specific treatment[7]. Early diagnosis of these conditions may facilitate effective management and prevention. This study was conducted to determine the prevalence of AR, and Ig and IgG subclass deficiency in preschool children with frequent URI.

Methods

This cross-sectional study was conducted during June to August 2006. The study protocol was approved by the research ethics committee of the Faculty of Medicine, Chiang Mai University.

Questionnaires were distributed to the parents of children aged 3-6 years in all kindergartens in Muang District, Chiang Mai, Thailand. The questionnaires consisted of 2 parts. Part 1 was about the frequency of URI in the previous 12

months, and Part 2 was the Thai translated version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Rhinitis was defined when a child had sneezing, or a runny or blocked nose with no evidence of a cold or flu in the previous 12 months. Parents answered the questionnaire at home and returned it within a few days. The prevalence of rhinitis was determined. The children who had had 10 or more episodes of URI within the previous year were defined as having frequent URI and invited to participate in the study[1]. The parents or guardians signed a written informed consent before the children were enrolled.

A history of rhinitis, wheezing, and atopic eczema in the participants, their parents and siblings was gathered by interview using the ISAAC questionnaire. Atopic eczema was defined as having had itchy recurrent rashes in the previous 12 months that were localized to flexural areas. The questions included the presence of wheezing in the previous 12 months. A family history of rhinitis, wheezing, or atopic eczema was defined as the participant's parents or siblings ever having had these complaints. Ten warning signs for primary immunodeficiency were evaluated. The presence of two or more warning signs indicated the need for further investigation.

The skin prick test (SPT) was performed according to the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) guidelines[8]. Six common aeroallergens and 2 common food allergens for young children (house dust mites, cockroaches, animal dander, cow's milk and egg white) were tested using standardized allergen extracts with a negative (glycerinated phenol-saline) and positive control (histamine 1 mg/ml) (Alk ABelló, Port Washington, NY, USA)[9-12]. Antihistamines were suspended for at least 7 days before testing, and the reaction was considered positive if a wheal of at least 3 mm greater in diameter than that of the negative control became apparent. Allergen sensitization was defined as having positive SPT for at least one allergen. Allergic rhinitis was diagnosed if the child met the criterion for rhinitis and positive SPT for at least one aeroallergen.

Blood samples were collected for Ig profiles. Serum IgG, IgA, IgM, IgE, IgG1, IgG2, IgG3, and IgG4 were measured by nephelometry (Dade Behring Inc., Newark, DE, USA). Ig deficiency was defined as having a serum level of less than two standard deviations below the mean for the relevant age group[13]. The diagnosis of selective IgA deficiency was made when the serum IgA level was 7 mg/dl or lower[14]. The relative distribution of IgG1, IgG2, IgG3, and IgG4 subclasses to the total IgG were considered to be normal if the proportion was 70:20:7:3[13]. For IgE, a level higher than 400 IU/ml in children more than 3 years of age was considered elevated[13].

Table 1. Demographic data of participating and non-participating children with frequent URI

Characteristic	Participants N=94	Non-participants N=125	P value
Age (years)	4.19±0.80	4.22±0.74	0.71[a]
Male gender	57 (60.60)	72 (57.60)	0.65[b]
Frequency of episodes (times per year)	15.04±9.24	15.58±8.23	0.54[c]
Prevalence of rhinitis by ISAAC	62 (65.96)	48 (38.40)	<0.01[a]

Note: Data shown in number (%) and mean ± SD

[a] Mann-Whitney U test

[b] Pearson Chi-square test

[c] The normal Approximation to Poisson Distribution

Means and standard deviations were computed for continuous variables, while percentages were computed for categorical variables. The risk factors for allergic rhinitis were analyzed by multiple logistic regressions. The significant effects of the explanatory variables and the interaction terms were subjected to likelihood ratio test.

Statistical analyses were performed using the Statistical Package for Social Science software (SPSS Inc., Chicago, IL, USA).

Results

Two thousand eight hundred and seventy-six questionnaires were distributed to 24 kindergartens. Two thousand three hundred and one (80.01 %) were returned. The average age of the children was 4.44 years (SD = 0.84). Fifty-six percent of them were male. The overall average frequency of URI was 4.71 episodes per year (SD = 4.71, ranging from 0 to 48 episodes per year, Mode = 3, Median = 3). The frequency of URI tended to decrease with age (5.22, 4.77, 4.04, and 3.44 episodes per year for ages 3, 4, 5, and 6 years, respectively). The prevalence of rhinitis in the previous 12 months was 28%.

Table 2. Results of skin prick test in the participants (N = 94)

Allergen	Positive result
Mite (*D. pteronyssinus*) 10000 AU/ml	39 (41.49)
Mite (*D. farinae*) 10000 AU/ml	24 (25.53)
American Cockroach 1:20 w/v	24 (25.53)
German Cockroach 1:20 w/v	3 (3.19)
Dog Epithelium 1:20 w/v	0 (0.00)
Cat Pelt 10000 BAU/ml	6 (6.38)
Cow's Milk 1:10 w/v	2 (2.18)
Egg White 1:100 w/v	1 (1.06)

Note: Data shown in number (%)

Two hundred and nineteen children (9.52%) met the criteria for frequent URI. Ninety-four (42.92%) of them participated in the study. There was no significant difference between the participants and non-participants, except for the former having a higher prevalence of rhinitis according to the ISAAC questionnaire (Table 1). There were 52 children (55.32%) whose SPT was positive; most of them (32/52) having multiple sensitizations. The results of SPTs are shown in Table 2. All children had a positive result for the histamine control, but none of them had a wheal reaction to glycerined phenol-saline control. House dust mite (*D. pteronyssinus*) was the most common allergen sensitizing the participants (41.49%). Three children were sensitized to food allergens as well as aeroallergens. No children were sensitized to dog epithelium.

Blood samples were collected from 93 children and measured for Ig profiles. Seventeen of them (18.28%) had high serum IgE levels. One child had a low serum IgA level (33 mg/dl), but did not meet the criteria for selective IgA deficiency. Two children had isolated IgG4 deficiency.

When the relative distribution of IgG subclasses to total IgG level was considered there are 44, 55, 81, and 22 children who had abnormally low IgG1, IgG2, IgG3, and IgG4 subclass percentages respectively. None of these children had a low IgG subclass for age.

According to the history and the results of the SPTs to aeroallergen, 40 children (42.55%) were diagnosed as AR, 22 had non-allergic rhinitis, and 12 had allergen sensitization, but did not meet the criterion for rhinitis according to the ISAAC questionnaire (Figure 1).

When participants definitely diagnosed as AR were compared with the group who were not, children with AR had significantly higher serum

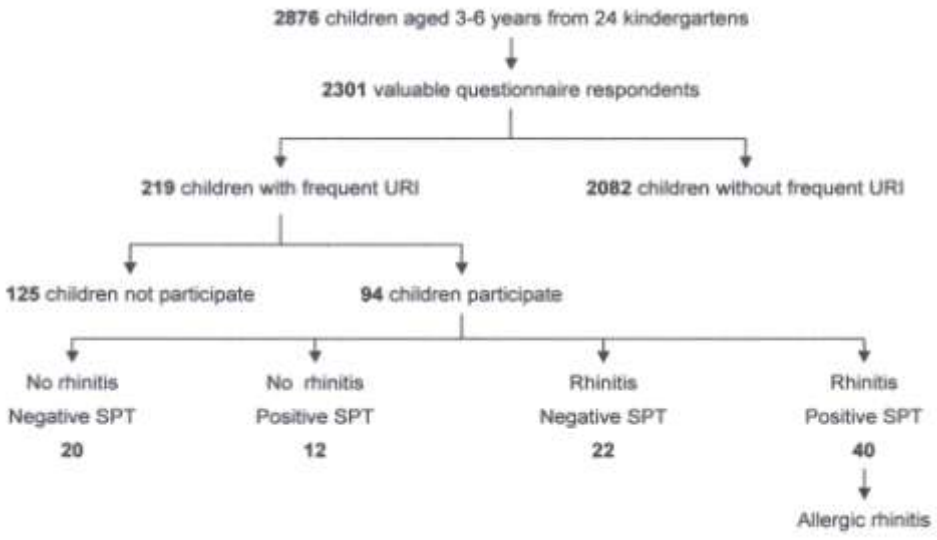

Figure 1. Summary of the study outcomes

Table 3. Comparison between participants with and without AR

Characteristic	AR N=40	No AR N=54	P value
Age (years)	4.37±0.76	4.06±0.81	0.06[a]
Male gender	28 (70.00)	29 (53.70)	0.11[b]
Serum IgE (IU/ml)	324±393	162±246	<0.01[a]
Frequency of episodes (times per year)	17.33±11.59	13.35±6.65	0.76[c]

Note: Data shown in number (%) and mean ± SD
[a] Mann-Whitney U test
[b] Pearson Chi-square test
[c] The normal Approximation to Poisson Distribution

IgE levels (Table 3). Exclusive breastfeeding for at least 6 months had a protective effect (adjusted OR = 0.17, 0.03-0.88), while paternal history of rhinitis was a risk factor (adjusted OR = 4.58, 1.36-15.40). However, passive smoking, history of wheezing or atopic eczema, and family history of wheezing or atopic eczema did not increase the risk of AR in this group of children (Table 4).

Nine children (9.57%) had 2 or more warning signs out of 10 for primary immunodeficiency. They were evaluated thoroughly and did not have obvious clinical features of immunodeficiency syndrome. When the participants who had 2 or more warning signs for primary immunodeficiency (Risk) were compared to those who had none (No risk), the risk group had significantly lower serum IgG and IgG2 levels. However, the IgG and IgG2 levels in both groups were within the normal range. So these differences had no clinical relevance.

Discussion

Previous studies have demonstrated that the average frequency of URI in preschool children varies from 3.5 to 9.8 episodes per year and usually had a reverse age related trend [1, 15, 16]. The average frequency in our study was 4.71 episodes per year with a tendency to decrease with age.

Since a study from Bangkok found that the incidence rate of acute respiratory infection in children aged 36-47 and 48-59 months was 9.8 and 8.8 per child per year, respectively[1], we defined a frequent URI as having 10 or more episodes within the previous year.

An SPT for common indoor allergens, i.e. house dust mites, cockroaches, and animal dander was carried out. Grass pollens and mold spore were not

Table 4. Factors that affected the prevalence of AR

Risk factor	AR N=40	No AR N=54	Adjusted OR	95% CI
Exclusive breastfeeding for ≥ 6 months	3 (7.50)	16 (29.63)	0.17	0.03-0.88
Passive smoking	18 (45.00)	20 (37.04)	1.98	0.74-5.30
History of wheezing in previous 12 months	9 (22.50)	10 (18.52)	1.18	0.33-4.18
History of eczema in previous 12 months	5 (12.50)	9 (16.67)	0.36	0.07-1.81
Family history of rhinitis by ISAAC				
Paternal rhinitis	12 (30.00)	7 (12.96)	4.58	1.36-15.40
Maternal rhinitis	11 (27.50)	14 (25.92)	1.24	0.43-3.61
Sibling rhinitis	9 (22.50)	8 (14.81)	0.98	0.27-3.56
Family history of wheezing by ISAAC*	5 (12.50)	4 (7.41)	2.16	0.34-13.62
Family history of eczema by ISAAC*	3 (7.50)	2 (3.70)	3.43	0.39-30.24

Note: * Anyone in the family (father, mother, or siblings) having had wheezing, or eczema. Data shown in number (%)

included because a previous study demonstrated that Chiang Mai children under 5 years of age, with AR and asthma, were not sensitized to these allergens[9]. About half (55.32%) of the children who participated in our study had allergen sensitization by preschool age and the most common one was house dust mite (*D. pteronyssinus*), which is consistent with other studies[9, 10].

In our study, the prevalence of AR, which was diagnosed by having a history of rhinitis in the previous 12 months and a positive SPT to at least 1 aeroallergen, was 42.55%. A previous study showed that the most established risk factor for AR was a family history of allergy, especially AR[17]. We also found that the paternal history of AR was a risk factor for allergic rhinitis. The existing evidence for early life risk factors related to AR is controversial and needs to be confirmed[6,

[18]. In our study, exclusive breastfeeding for at least 6 months had a protective effect against AR.

In our study, 22 children (23.40%) who had a history of rhinitis in the previous 12 months, but negative SPT, were classified as non-allergic rhinitis. Furthermore, some of them also had a striking family history of rhinitis, wheezing, or atopic eczema. Previous studies have demonstrated that a proportion of negative SPT patients have nasal eosinophilia and a positive nasal allergen provocation test[19, 20]. Local immunoglobulin E (IgE) production is one of the possible explanations for this finding[20]. For a definite diagnosis of this group of our participants, further investigations should be done, i.e. the SPT for other aeroallergens (molds and pollens), nasal cytology (nasal smear or nasal scraping), and the nasal provocation test.

Susceptibility to respiratory infections has been linked to Ig and IgG subclass deficiency, but the clinical relevance of IgG subclass deficiency is controversial[7]. Most previous studies were conducted in patients with recurrent or chronic rhinosinusitis, and IgG and IgG subclass deficiencies, with or without abnormal antibody response to pneumococcal vaccine were identified as underlying etiologies[21, 22]. In our study, most preschool children with frequent URI had normal IgG and IgG subclass levels except for 2, who had isolated IgG4 deficiency which was of no clinical relevance[7]. However, we found that many children had abnormal low IgG1, IgG2, IgG3, and IgG4 subclass percentage. Further studies should be done to find out whether these abnormal proportions have a clinical relevance.

In conclusion, the frequency of URI tends to decrease with age. The prevalence of AR in preschool children with frequent URI in our study was 42.55%. AR should be considered if there is a family history of allergic rhinitis, especially in the father. Exclusive breastfeeding for at least 6 months has a protective role against AR. Because immunoglobulin deficiency was not found in our study, measurement of serum Ig and IgG subclass levels should be considered only in a preschool child who have obvious clinical features of immunodeficiency other than frequent URI.

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