

Factors Associated with Childhood Non-Atopic Asthma

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Objective: To determine factors associated with childhood non-atopic asthma comparing to those with atopic asthma

Materials and Methods: A cross-sectional study was conducted among asthmatic pediatric patients aged between 1 month and 15 years of age who were treated between 2008 and 2013 at Department of Pediatrics, Charoenkrung Pracharak Hospital. Positive skin prick test with at least 1 allergen indicated atopic asthma whereas the negative test indicated non-atopic asthma. Population characteristics and factors associated with non-atopic asthma were compared with atopic group.

Results: Of 373 childhood asthmatic patients studied, 189 (50.7%) had non-atopic asthma. Median age at onset and median age of non-atopic asthmatic patients were significantly younger than atopic asthmatic patients: 1.16 ± 1.29 years vs. 2.18 ± 1.99 years ($p < 0.001$) and 2.91 ± 2.08 years vs. 5.45 ± 3.33 years ($p < 0.001$), respectively. Factors associated with a significantly greater risk of non-atopic comparing to atopic asthma included age at onset < 1 year old, a history of wheezing associated with upper respiratory tract infection, and a history of breastfeeding > 6 months.

Conclusion: Factors associated with a greater risk of non-atopic asthma were age at onset < 1 year old, a history of wheezing associated with upper respiratory tract infection, and a history of breastfeeding > 6 months.

Keywords: Non-atopic asthma, Risk factors

J Med Assoc Thai 2018; 101 (Suppl. 8): S111-S117

Website: <http://www.jmatonline.com>

Asthma is characterized by chronic airway inflammation which can cause death and disability. A global prevalence ranged from 1% to 16% of the population in different countries⁽¹⁾. The prevalence of asthma is more common in developed than in developing countries⁽²⁾. One study from Thailand showed the prevalence of asthma in the younger age group (6 to 7 years old) had increased from 12% to 15%⁽³⁾.

The International Study of Asthma and Allergies in Childhood Phase III which clearly demonstrated a very high prevalence of asthma in low socioeconomic conditions suggested an important role for the local environment on the occurrence of asthma. The interactions between multiple genes and the

environment, through both allergic and non-allergic mechanisms, certainly impacted on the prevalence across the regions⁽⁴⁾.

Many studies found correlation of asthma and atopy⁽⁵⁻⁸⁾. The strength of the associations increased with economic development^(5,6). Atopy is one of the main risk factors for the severity and persistence of disease⁽⁷⁾. However, not all patients with asthma were related to atopy because several distinct wheezing phenotypes in childhood were not found to have atopy. Also an avoidance of allergen in early life to prevent atopic sensitization did not have definitive lasting benefits⁽⁶⁾.

Distinct patterns of risk factors for atopic and non-atopic asthma in children and adolescents have been reported in several studies. Non-atopic asthma was associated with recurrent chest infection at 2 years⁽⁶⁾, lower respiratory tract infection in childhood⁽⁵⁾, maternal asthma^(6,9), family history of asthma/rhinitis/eczema⁽⁵⁾, male sex⁽⁹⁾, maternal smoking^(9,10), mold or dampness at home^(5,9,10), and < 3

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How to cite this article: Benjasupattananun P, Achararit N, Manavathongchai M. Factors Associated with Childhood Non-atopic Asthma. J Med Assoc Thai 2018;101;Suppl.8: S111-S117.

months of breast feeding⁽¹⁰⁾. In Thailand, few studies have been conducted on non-atopic asthma.

Currently, abundant information exists regarding adult non-atopic asthma, whereas there are fewer data in children. We aimed to determine the clinical differences between non-atopic and atopic asthma in children.

Materials and Methods

This cross-sectional study was approved by the Ethics Committees of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University and Bangkok Metropolitan Administration. Asthmatic patients who were treated in the institution between 2008 and 2013 were identified. Inclusion criteria were children between 1 month to 15 years old with a diagnosis of asthma according to the Global Initiative for Asthma guidelines⁽¹¹⁾. Asthma was grouped as atopic or non-atopic according to the results of skin prick test [SPT]. Positive SPT for at least 1 allergen indicated atopic asthma and negative test indicated non-atopic asthma. Exclusion criteria were those who had underlying disease that might cause wheezing e.g., heart disease, chronic lung disease, subglottic stenosis, and had incomplete data.

The SPT was performed with 7 common aeroallergens and 6 common food allergens in patients <3 years old, and with 11 common aeroallergens in older patients. Histamine and saline were used as positive and negative controls. After 15 minutes, the wheal diameter was measured, with positive results being a diameter of at least 3 mm greater than that in the negative controls.

Data collected were general characteristics and demographic factors such as age, sex, mode of delivery birth weight, any event during perinatal period, age onset of asthma, history of maternal smoking during pregnancy, history of breastfeeding, day care, obesity, gastroesophageal reflux disease, family history of asthma, allergic rhinitis, smoking in the house, and history of allergen exposure and asthma features.

Breastfeeding included breastfeeding with or without supplementary milk or food.

Statistical analysis

Study population characteristics and factors associated with atopic or non-atopic asthma were evaluated. Student's t-test or Mann-Whitney U test was used to compare variables and were used in a logistic model to define the independent predictors of non-atopic asthma by multivariate analysis $p < 0.05$ was considered statistically significant.

Results

Among 373 asthmatic patients who were enrolled into the study between 2008 and 2013, 189 (50.7%) had non-atopic asthma. Demographic data of the patients are summarized in Table 1. Non-atopic asthmatic patients were significantly younger than atopic asthmatic patients (2.91 ± 2.08 years vs. 5.45 ± 3.33 years, $p < 0.001$). The corresponding age at onset were 1.16 ± 1.29 years and 2.18 ± 1.99 years ($p < 0.001$).

We studied the association of several demographic factors and childhood non-atopic and atopic asthma (Table 2). Patients with breastfeeding: >6 months had a significantly higher risk of non-atopic asthma than atopic asthma.

We studied the history of allergen exposure in childhood with non-atopic and atopic asthma. These are summarized in Table 3. There were no significant difference between the history of allergens exposure and the atopic or non-atopic asthma. Asthma features in childhood with non-atopic and atopic asthma are summarized in Table 4. Patients with age of onset 1 to 5 years was a significant protective factor of non-atopic asthma compared to age of onset <1 year. In the other hand meant that patients with age of onset <1 year was a significant risk factor of non-atopic asthma compared to age of onset 1 to 5 years.

Discussion

The results show that non-atopic asthma was

Table 1. General characteristics and continuous data of childhood non-atopic and atopic asthma

	Non-atopic asthma (n = 189)	Atopic asthma (n = 184)	p-value
Age (months)	34.94±24.95	65.35±40.00	<0.001
Birth weight (kg)	2.97±0.58	2.96±0.54	0.085
Breastfeeding (months)	8.95±10.32	7.02±10.29	0.070
Onset of disease (months)	13.88±15.47	26.10±23.91	<0.001
Day care (months)	4.35±10.61	2.42±8.42	0.057

Table 2. Univariate and multivariate analyses of demographic factors associated with childhood non-atopic and atopic asthma

Factor associated with childhood asthma	Childhood asthma		Univariate			Multivariate		
	Non-atopic (n = 189)	Atopic (n = 184)	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Sex: Male	123	111	1.22	0.81 to 1.92	0.343	1.00	0.61 to 1.74	0.991
Birth weight: <2,500 gm	32	24	1.44	0.8 to 2.42	0.303	1.33	0.60 to 3.00	0.554
Mode of delivery:								
Cesarean section	42	63	0.53	0.42 to 0.94	0.010	0.63	0.38 to 1.18	0.145
Preterm	13	5	2.90	0.99 to 8.31	0.054	1.31	0.31 to 5.36	0.738
Complications during perinatal period								
On O ₂ , Pneumonia, Pneumothorax	5	4	1.42	0.4 to 5.19	0.741	1.19	0.31 to 5.42	0.823
Jaundice	41	35	1.30	0.81 to 2.21	0.333	1.12	0.62 to 2.02	0.771
Other complications	10	8	1.44	0.51 to 3.57	0.515	0.67	0.21 to 2.43	0.603
History of attending daycare	39	20	2.22	1.21 to 3.87	0.008	2.00	0.98 to 4.11	0.054
Length of breastfeeding: >6 months	69	45	1.81	1.21 to 2.82	0.009	2.03	1.11 to 3.44	0.015
Allergic rhinitis	69	100	0.48	0.32 to 0.74	0.001	0.82	0.54 to 1.33	0.335
Gastroesophageal reflux disease	5	1	5.01	0.62 to 43.02	0.215	3.51	0.31 to 39.73	0.314
Obesity	32	44	0.65	0.44 to 1.10	0.094	1.22	0.62 to 2.23	0.662
Family history of asthma	45	50	0.79	0.47 to 1.31	0.456	0.81	0.33 to 2.01	0.619
Smoking during pregnancy	4	1	3.91	0.41 to 35.71	0.372	6.12	0.51 to 82.01	0.171
Smoking in a house	109	110	0.91	0.64 to 1.41	0.679	0.92	0.54 to 1.45	0.506
Factory nearby a house	38	34	1.12	0.73 to 1.91	0.690	0.89	0.52 to 1.72	0.660

Table 3. Univariate and multivariate analyses of history of allergen exposure in childhood with non-atopic and atopic asthma

Factor associated with childhood asthma	Childhood asthma		Univariate			Multivariate		
	Non-atopic (n = 189)	Atopic (n = 184)	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Pet in a house	57	63	0.76	0.46 to 1.32	0.399	1.02	0.63 to 1.71	0.976
Use of cloth duster	6	12	0.51	0.24 to 1.32	0.132	0.73	0.21 to 2.32	0.534
Bed sheets washed every week	148	132	1.44	0.92 to 2.32	0.143	1.22	0.56 to 2.09	0.632
Doll in a bedroom	76	68	1.24	0.76 to 1.74	0.519	1.04	0.62 to 1.73	0.903

Table 4. Univariate and multivariate analyses of asthma features in childhood with non-atopic and atopic asthma

Factor associated with childhood asthma	Childhood asthma		Univariate		Multivariate			
	Non-atopic (n = 189)	Atopic (n = 184)	Odds ratio	95% CI	p-value	Odds	95% CI	p-value
Age at onset								
<1 year	104	45	1.00	reference		1.00	reference	
1-5 year	82	127	0.32	0.21 to 0.43	<0.001	0.32	0.22 to 0.50	<0.001
>5-10 year	3	12	0.14	0.02 to 0.44	<0.001	0.68	0.11 to 4.32	0.674
History of wheezing associated with URI	131	88	2.50	1.61 to 3.82	<0.001	2.01	1.22 to 3.52	0.010
History of ICU admission with wheezing	7	6	1.10	0.44-3.50	0.816	0.71	0.21 to 2.56	0.564
Frequency of wheezing before diagnosis								
Every >4 months	19	33	1.00	reference		1.00	reference	
Every 3-4 months	65	56	2.02	1.03 to 3.93	0.038	1.72	0.74 to 4.29	0.242
Every <3 months	105	95	1.92	1.02 to 3.60	0.040	1.60	0.74 to 3.72	0.249
History of admission with wheezing	130	124	1.11	0.68 to 1.68	0.716	0.82	0.51 to 1.41	0.472
Severity								
Mild intermittent	117	94	1.00	reference		1.00	reference	
Mild and moderate and severe persistent	72	90	0.64	0.44 to 0.97	0.035	0.92	0.63 to 1.54	0.745
Asthma symptom control								
Uncontrolled and partly controlled	72	70	1.00	reference		1.00	reference	
Controlled	117	114	1.04	0.71 to 1.49	0.992	1.30	0.72 to 2.53	0.433
Controlled medication								
Budesonide 400 mcg/day	106	109	1.00	reference		1.00	reference	
Budesonide 800 mcg/day	2	1	2.14	0.22 to 23.03	0.620	9.22	0.54 to 155.70	0.126
Fluticasone	4	8	0.54	0.22 to 1.84	0.281	0.75	0.22 to 3.33	0.701
Leukotriene antagonist	3	1	3.10	0.32 to 30.11	0.369	1.87	0.09 to 32.04	0.645
Combination inhaled CS and LABA	49	47	1.12	0.70 to 1.73	0.777	1.44	0.67 to 3.02	0.322
Inhaled CS and Leukotriene antagonist	22	15	1.52	0.74 to 3.05	0.254	1.05	0.45 to 2.81	0.759

URI, upper respiratory tract infection; CS, corticosteroid; LABA, long-acting beta2 agonist; ICU, intensive care unit

as frequent as atopic asthma in Thai asthmatic children between 1 month and 15 years of age. Approximately 50.7% of cases were classified as non-atopic asthma. In contrast, previous studies from Iran⁽¹²⁾ and Chile⁽¹³⁾ reported rates of 21.1% and 37.5%, respectively, for non-atopic asthmatic children^(12,13). Moreover, non-atopic asthmatic children were significantly younger than atopic asthmatic children, which was similar to the results of a previous study in Iran⁽¹²⁾.

The present study showed that asthmatic children with a history of breastfeeding for >6 months had a higher risk of non-atopic asthma. Previous findings by Nwaru et al⁽⁷⁾ also found longer breastfeeding period (5 to 9.5 months) also had greater risk than that with a duration of <5 months⁽⁷⁾.

We found non-atopic asthmatic children had significantly younger age at onset of asthma than that of atopic asthmatic children. Similar to the study of Castro-Rodriguez et al⁽¹³⁾, the onset of symptoms was significantly earlier in non-atopic asthmatic children than in atopic asthmatic children. In contrast, two studies from Iran and the United Kingdom showed that ages at onset were not different between atopic and non-atopic asthmatic patients^(6,12). Asthma began in early childhood, which was often linked to exposure to allergens, such as dust mites, tobacco, smoke, and viral respiratory infections. In very young children (<2 years old), the definite diagnosis of asthma was difficult. Wheezing at this age often followed a viral infection which might disappear later.

An important factor associated with non-atopic asthma in our study was a history of wheezing associated with upper respiratory tract infection [URI] had a significantly higher risk of non-atopic asthma than those without such a history. Kurukulaaratchy et al⁽⁶⁾ also found that patients with recurrent chest infections in infancy showed a significantly increased risk of non-atopic asthma⁽⁶⁾. From a systematic review of the risk factors for non-atopic asthma/wheeze in children and adolescents, a positive association between lower respiratory symptoms or infections and non-atopic asthma in early childhood⁽⁵⁾. Non-atopic asthma was usually secondary to chronic or recurrent infection of the bronchi, sinuses, or tonsils and adenoids. There was evidence that it developed from hypersensitivity to the bacteria or, more commonly, viruses that caused the infection⁽¹⁴⁾. Respiratory tract infections were found to have a causal role in non-atopic asthma development through an impaired epithelial barrier, antiviral immune responses, or other underlying mechanisms that cause damage to, and

remodeling of, the airways in susceptible children⁽¹⁵⁾, whereas atopic asthma damage and remodeling of the airways has been found to occur due to allergen-induced inflammatory cytokine release. It should be noted that the inflammatory process in the airways was similar between atopic and non-atopic asthma patients. However, there were differences regarding antigen exposure⁽¹⁶⁾. Microbial super-antigens may also be important in non-atopic asthma, driving the inflammatory process in the airways.

Furthermore, our study showed that a family history of asthma, smoking during pregnancy, and smoking in the house were not significantly associated with non-atopic asthma. These findings were different from those of most previous studies^(5,9,17). A family history of asthma showed a consistently high and significantly positive association with non-atopic asthma in one systematic review⁽⁵⁾. All these studies suggested that a family history of asthma is associated with non-atopic asthma. However, a family history of asthma was not significantly associated with non-atopic asthma in our study because we found that a family history of asthma was similarly associated with both groups of non-atopic with atopic asthma.

Mode of delivery and sex of children were not significantly different between the two groups, similar to the findings of Mahdavian et al⁽¹²⁾. However, Moncayo et al⁽¹⁷⁾ found males had significantly greater risk of atopic wheezing. Other factors, such as environment, history of daycare, obesity, birth weight, comorbidities (e.g. allergic rhinitis, gastroesophageal reflux disease), severity of disease, and control of disease, were not associated with childhood non-atopic asthma, similar to the results of most earlier studies^(5,12,17).

A limitation of the present study was the use of the control group because there were a wide variety of control groups from different studies, such as non-atopic, non-asthma, and non-asthma irrespective of atopy or atopic asthma groups. Therefore, many difference of control groups might result in different causal factors.

Conclusion

In summary, the present study showed that approximately 50% of asthmatic children between 1 month and 15 years of age had non-atopic asthma. Factors associated with a greater risk of non-atopic asthma included age at onset <1 year, a history of wheezing associated with URI, and a history of breastfeeding for >6 months. Other factors, however,

such as environment, history of daycare, obesity, birth weight, comorbid disease (e.g. allergic rhinitis, gastroesophageal reflux disease), severity of disease, asthma symptom control, and types of control medication, were not associated with childhood non-atopic asthma.

What is already known on this topic?

Several risk factors for atopic and non-atopic asthma in children and adolescents have been reported. Non-atopic asthma was positively associated with recurrent chest infection at 2 years, lower respiratory tract infection in childhood, maternal asthma, family history of asthma/rhinitis/eczema, male sex, maternal smoking, mold or dampness at home, and <3 months of breastfeeding.

What this study adds?

Factors associated with risk of non-atopic asthma in Thai children included age at onset <1 year, a history of wheezing associated with URI, and a history of breastfeeding for >6 months.

Acknowledgements

The authors would like to thank all the staffs in the Department of Pediatrics, Charoenkrung Pracharak Hospital, Bangkok Metropolitan Administration for their cooperation and all the pediatric subjects recruited in the study.

Potential conflicts of interest

The authors declare no conflict of interest.

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