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Risk factors of wheeze and allergy after lower respiratory tract infections during early childhood

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Lower respiratory tract infections (LRIs) during early childhood can lead to bronchial hyperreactivity or recurrent obstructive bronchitis. The role of LRIs in the pathogenesis of allergic diseases such as allergic rhinoconjunctivitis, atopic eczema, and bronchial asthma is less clear. The aim of this retrospective study was to determine the incidence of subsequent wheezing and atopy, and the known risk factors for allergic sensitization in 74 children hospitalized for acute LRIs of various etiologies from January 1994 through December 1994. Results showed that there are no differences in outcomes between patients with respiratory syncytial virus LRI, *Chlamydia pneumoniae* LRI, and LRIs caused by other agents. Although lower respiratory tract illnesses, especially those caused by respiratory syncytial virus during infancy, were associated with an increased risk of subsequent wheezing during early childhood, wheezing tended to disappear with increasing age in many children. This study also found recurrent episodes of wheezing during the first 5 years of life, and symptoms suggestive of allergic rhinoconjunctivitis were the only factors predictive of subsequent diagnosis of asthma for children who had LRIs during early childhood. In conclusion, this study suggests that prevention of recurrent wheezing LRIs and good control of allergic rhinoconjunctivitis is critical for preventing subsequent development of bronchial asthma.

Key words: Allergy, asthma, *Chlamydia pneumoniae*, respiratory syncytial virus

Acute respiratory tract infection is the most common disease in infants and young children, with respiratory syncytial virus (RSV) being its most common cause [1-3]. The clinical presentations vary from mild respiratory tract infection to severe bronchiolitis. Many studies with different designs and aims have shown that lower respiratory tract infections (LRIs) in young children are often followed by repeated wheezing episodes. At least 50% of children studied had repeated wheezing episodes, regardless of whether the population had confirmed etiology such as RSV or was recruited according to clinical symptoms [2-4]. Many studies have focused on RSV, which has been suggested to be more likely to induce wheezing later than other viruses [4,5]. Some researchers have suggested that RSV lower respiratory tract illnesses are associated with increased risk of subsequent allergic sensitization, but the association is still inconclusive [6,7]. The roles of viral respiratory infections and the development of allergic diseases are nevertheless complex and controversial. Certain infections such as *Chlamydia pneumoniae* of the immature airway may be sensitized to environmental allergens, whereas some viruses may cause airway damage and hyperreactivity in the bronchial tree [8,9]. In 1989, Frudén *et al* [10] first reported a case of serologically diagnosed acute *C. pneumoniae* infection that progressed to chronic asthmatic bronchitis. Hahn *et al* [11] also showed that acute *C. pneumoniae* respiratory tract infections in previously unexposed, nonasthmatic individuals resulted in chronic asthma. Researchers have shown that a variety of respiratory pathogens including RSV and *C. pneumoniae* triggered acute wheezing illnesses [1-3,12].

The aim of this study was to investigate the relationship between initial LRIs and RSV, *C. pneumoniae*, and other etiologies during early childhood, and the subsequent development of wheezing and allergies during late childhood. Other known risk factors related to the subsequent development of wheezing and allergic diseases during late childhood were also analyzed.

Materials and Methods

Patients collection

From January 1994 through December 1994, a total of 74 children younger than 2 years (range, 1-24 month)

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hospitalized at the National Taiwan University Hospital with lower respiratory infections were included in this retrospective study. The inclusion criteria were a clinical diagnosis of LRI and no history of similar illness. All patients had cough, tachycardia, and poor appetites associated with hyperinflation, recession, fine crepitation, and often rhonchi.

Children born prematurely or had severe congenital diseases such as severe congenital heart disease, severe airway anomaly, and metabolic disease were excluded. Their medical charts were reviewed and data including age, sex, laboratory findings, and treatment were recorded. Respiratory syncytial virus infection and chlamydial infection (strain TWAR) were initially documented in all patients using identification of antigens in nasopharyngeal secretions. Children were divided into 3 groups according to the cause of initial lower respiratory tract illness during their first 2 years of life. Group I children had RSV, Group II had *C. pneumoniae*, and Group III had negative tests for RSV and *C. pneumoniae*. A follow-up questionnaire was administered to the parents of all children older than 5 years. The questions pertained to episodes of wheezing, diagnosis of asthma or allergic rhinoconjunctivitis, subsequent hospitalization for respiratory problems, and family smoking habits. Hereditary and environmental risk factors were also documented. From the case records, we extracted information regarding (1) family history, including atopic symptoms of parents and siblings, (2) environmental factors, including number of siblings, people smoking, and pets in the home; and (3) subsequent development of wheezing and allergic symptoms in children older than 5 years. Children older than 5 years were considered to have symptoms suggestive of asthma if they reported one or more of the following: coughing and wheezing at night in the absence of upper respiratory infection (URI), coughing and wheezing on exertion, wheezing or whistling sound in the chest with or without URI, and doctor-diagnosed asthma.

Children who had sneezing, runny, or obstructed noses accompanied by itchy-watery eyes but without diagnoses of a cold or flu were considered to have allergic rhinoconjunctivitis. Children with itchy rashes that affected areas at the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes were considered to have atopic eczema.

Statistical analysis

Results were analyzed using the chi-square test for categorical variables, and the Fisher's exact test was used when the expected frequency for any cell was less than 5. The Mann-Whitney U test was used for variables that were not normally distributed. A p value of less than 0.05 was considered statistically significant.

Results

The mean age at onset of the 74 children enrolled into this study was 7.24 ± 5.19 months (range, 1-24 months); 42 (56.8%) of the 74 patients were boys. Of the 74 children, RSV LRI was diagnosed in 20 (27%) patients, and *C. pneumoniae* LRI was diagnosed in 9 (12.2%) patients. Table 1 shows the analysis of the 3 groups according to clinical details along with family characteristics. Children with RSV LRI (Group I) were younger than those in the other 2 groups, but the difference was not statistically significant.

The number of children who were fed breast milk for more than 2 months was small; only 3 (4%) of 74 patients were fed breast milk for more than 2 months. Thirty-five (47.3%) of the 74 children enrolled had

Table 1. Patient characteristics

	Group I n = 20	Group II n = 9	Group III n = 45
Onset age, month (range)	5.5 ± 5.2 (1-24)	9.8 ± 5.6 (3-20)	7.3 ± 4.9 (1-24)
Male/female ratio	11:9	7:2	24:21
Breast feeding >2 months (%)	1 (5)	0	2 (4.4)
Family history of atopy[a] (%)	9 (45)	3	23 (51.1)
Family history of asthma[a] (%)	2 (10)	1	8 (17.8)
Passive smoking exposure in the home (%)	9 (45)	2	20 (44.4)
Furry pets in the home (%)	2 (10)	1	3 (6.7)
Siblings in the home (range)	1.7 (1-3)	1.2 (1-2)	1.5 (0-3)

Note: Group I = children with initial respiratory syncytial virus lower respiratory tract infection; Group II = children with *C. pneumoniae* lower respiratory tract infection; Group III = children with lower respiratory tract infection but tests for respiratory syncytial virus or *C. pneumoniae* were negative.

[a]Positive family history was defined when asthma, allergic rhinoconjunctivitis, or atopic dermatitis was diagnosed by a doctor in anyone of the first-degree relatives.

Table 2. Cumulative incidences of atopic symptoms in percentage in the 3 groups

Outcome	Group I n = 20 (%)	Group II n = 9	Group III n = 45 (%)
Repeated wheezing during the first 5 yr of life (≥2 episodes)	16 (80)	6	25 (55.5)
Readmission for LRI during the first 5 yr of life	9 (45)	5	13 (28.9)
Atopic asthma ≥5 yr of age	4 (20)	2	11 (24.4)
Allergic rhinoconjunctivitis ≥5 yr of age	6 (30)	4	15 (33.3)
Atopy[a] ≥5 yr of age	7 (35)	5	18 (40)

Abbrevation: LRI = lower respiratory track infection

[a]Atopic asthma, allergic rhinoconjunctivitis, and/or atopic eczema (atopic symptoms in at least one organ).

family history of atopy. Only 11 (14.9%) of the patients enrolled in this study had family history of asthma. The number of children who had passive smoking exposure at home was 41.9%. Only 6 (8.1%) of the 74 children enrolled in this study had furry pets in the home. There were no other major differences between the 3 groups with respect to patient characteristics and environmental risk factors. There was no difference in outcomes among the 3 groups (Table 2).

Subsequent wheezing during the first 5 years of life was more frequent in children with initial RSV or *C. pneumoniae* LRI (groups I and II) than in Group III (80% and 66.7% vs 55.5%). Although the rehospitalization rate for LRI of children with initial RSV or *C. pneumoniae* LRI (groups I and II) was higher than that of Group III (45% and 55.6% vs 28.9%), the difference did not reach statistical significance. At follow-up visit, 63% (47/74) of the postbronchiolitis children had subsequent wheezing during the first 5 years of life. A total of 23% (17/74) of the children had symptoms suggestive of asthma, and 33.8% (25/74) were considered to have allergic rhinoconjunctivitis after they have reached the age of 5 years. No relationship was demonstrated between the different etiologies of LRI and subsequent atopic status including asthma, allergic rhinoconjunctivitis, and eczema.

There was a high incidence of positive family history of atopy (47.3%) and passive smoking exposure (47.3%) in the children with a diagnosis of asthma aged more than 5 years. However, no relationship was demonstrated between the clinical diagnosis of asthma and family history of atopy or passive smoking exposure (Tables 3 and 4). Limited by the small sample size, there was no relationship demonstrated between clinical diagnosis of asthma and recurrent early childhood wheezing or diagnosis of allergic rhinoconjunctivitis in Group II.

It is noteworthy that 16 (94.1%) of 17 children diagnosed with asthma aged 5 years or above had repeated episodes of wheezing during the first 5 years of life, compared with 31 (54.4%) of 57 children who had no asthma after 5 years of age ($p<0.05$). Thirteen (76.5%) of 17 individuals with a diagnosis of asthma after 5 years of age had allergic rhinoconjunctivitis, compared with 12 (21.1%) of 57 children who had no asthma after 5 years of age ($p<0.05$).

Discussion

In this study, there was no significant difference in the prevalence of known risk factors for wheezing and allergies between children with LRIs caused by RSV, *C. pneumoniae*, and those with negative test results for

Table 3. Percentages of atopic heredity, environmental factors, recurrent wheezing during early childhood in the different subgroups of groups I, II, and III

	Group I (n = 20)		Group II (n = 9)		Group III (n = 45)	
	Asthma n = 4	Nonasthma n = 16 (%)	Asthma n = 2	Nonasthma n = 7	Asthma n = 11 (%)	Nonasthma n = 34 (%)
Family history of atopy	2	7 (43.7)	1	2	6 (54.5)	18 (52.9)
Family history of asthma	0	2 (12.5)	1	0	3 (27.3)	6 (17.6)
Passive smoking exposure in the home	3	8 (50.0)	2	2	7 (63.6)	15 (44.1)
Furry pets in the home	0	2 (12.5)	1	0	1 (9.1)	2 (5.9)
Rewheezing <5 yr of age (≥2 episodes)	4[a]	12 (75)	2	4	10 (90.9)[a]	15 (44.1)
Rehospitalization for LRI <5 yr of age	1	8 (50.0)	2	3	5 (45.5)	8 (23.5)
Allergic rhinoconjunctivitis ≥5 yr of age	4[a]	2 (12.5)	1	3	8 (72.7)[a]	7 (20.6)

Abbreviation: LRI = lower respiratory tract infection

[a]$p<0.05$ (2-sided Fisher's exact test), asthma subgroup was compared with non-asthma subgroup in individual groups.

Table 4. Percentages of atopic heredity, environmental factors, recurrent wheezing during early childhood in the different groups (asthma vs nonasthma)

	Asthma n = 17 (%)	Nonasthma n = 57 (%)	*p*
Family history of atopy	8 (47.1)	27 (47.4)	NS
Family history of asthma	4 (23.5)	8 (14)	NS
Passive smoking exposure at home	10 (58.8)	25 (43.9)	NS
Furry pets in the home	2 (11.8)	4 (7)	NS
Rewheezing <5 yr of age (≥2 episodes)	16 (94.1)	31 (54.4)	<0.05
Rehospitalization for LRIs <5 yr of age	8 (47.1)	19 (33.3)	NS
Allergic rhinoconjunctivitis ≥5 years of age	13 (76.5)	12 (21.1)	<0.05

Abbreviation: NS = not significant

both agents. During early childhood, most lower respiratory tract illnesses with wheezing are associated with infection caused by RSV [1-3]. Twenty (26%) of the 74 patients enrolled in this study were given a diagnosis of definitely RSV LRI. Children enrolled into this study had severe symptoms and required hospitalization. Of all children with LRI enrolled in this study who had increased risks for severe symptoms with respiratory tract infections, 42 (56.8%) were boys. This was consistent with the results of previous studies, which demonstrated that boys were more likely to have smaller airways for their lung size than girls, and this potentially put them at increased risk for respiratory tract infections [13,14]. There may be anatomical reasons that boys have more severe lower respiratory tract symptomatology during infections than girls.

In 1991, Holberg *et al* [15] demonstrated that children who had minimal amounts of breast-feeding were especially at risk for RSV-LRIs during the first 5 months of life. In this study, only one (5%) of 20 children with initial RSV LRIs had received breast milk for more than 2 months. The numbers of children who had received breast milk for more than 2 months was small (only 3 in all 74 children). Because of the small sample size and lack of healthy controls, this study could not demonstrate whether breast milk protects infants from RSV infections and other LRIs.

Results of previous studies have demonstrated a highly significant relation between parental smoking, LRIs and wheezing illnesses in atopic babies [16,17]. Contradictorily, results of some other studies showed no effects of passive smoking exposure in infants hospitalized with acute bronchiolitis compared with healthy controls [15,18]. Parental smoking rate was high (41.9%) in this study, but no significant associations were noted between passive smoking and the development of bronchial asthma.

It remains unclear whether viral LRIs cause increased airway liabilities, and whether children with a genetic predisposition to atopy are more likely to develop LRIs and/or subsequent allergic symptoms. Many researchers have shown that LRIs in young children are often followed by repeated wheezing episodes [4,5,12]. Most infectious agents elicite immune responses characteristic of Th1-related cytokine profile, which is only rarely accompanied by the manifestations of allergies [19-21]. Welliver *et al* [22] demonstrated a higher prevalence of specific immunoglobulin (Ig) E against RSV in the nasal secretions of infants with RSV LRI who wheeze than those who did not. Previous experimental animal studies have implicated Th-2 responses to the G-protein of RSV and resulting pulmonary eosinophilia [23]. This may explain why children with initial RSV LRI tended to experience recurrent wheezing during early childhood.

Previous retrospective studies have reported a 40% to 50% incidence of wheezing in children following hospitalization as a result of RSV bronchiolitis [24-26]. In 1989, Sly and Hibert [27] demonstrated that more than 90% of infants had symptoms suggestive of asthma during the 5 years following their initial illness. In this study, 16 (80%) of 20 children with initial RSV LRI developed recurrent wheezing during the first 5 years of life. These results are consistent with those of previous studies.

Although several previous studies have demonstrated that acute *C. pneumoniae* respiratory tract infections have resulted in chronic asthma during late childhood and adulthood [10,11], no significant relationship between initial *C. pneumoniae* infection and subsequent development of asthma was found in this study. However, results of this study should be interpreted carefully because of the small sample size and lack of healthy controls for comparison. This study did not demonstrate any relationship between subsequent development of allergic symptoms including asthmatic wheezing and initial LRIs with different pathogens (RSV, *C. pneumoniae*, or others), although

there was a trend for children with initial RSV LRIs to experience wheezing and high readmission rates for other episodes of pulmonary disease during the first 5 years of life. Stein *et al* [28] demonstrated that children with lower respiratory tract illnesses before the age of 3 years were associated with significant increases in the risk of subsequent wheezing during the first 10 years of life. The association subsides rapidly with age, and become insignificant by the age of 13 years. Children in this study had symptoms such as wheezing more frequently during the first 5 years of life, and the symptoms subsided with age. This finding was consistent with the results of most previous studies, which showed that the majority of infants with wheezing had transient conditions associated with diminished airway functions and did not have increased risks of asthma or allergies later in life [28-31]. Forty-seven (63%) of 74 children enrolled in this study had subsequent recurrent wheezing during the first 5 years of life, but only 23% of all children had symptoms suggestive of asthma after the age of 5 years. Children who were classified as RSV and *C. pneumoniae* negative during the acute episode had the same patterns of symptomatology as those in the other 2 groups who were RSV or *C. pneumoniae* positive.

Many researchers have suggested that family history of atopy and asthma, as well as environmental factors including passive exposure to cigarette smoke and furry pets, may have an important role in determining the long-term outcomes of children with initial LRIs [32-34]. This study failed to detect any significant relationship between family history of atopy and asthma, environmental factors including passive exposure to cigarette smoke and furry pets, and subsequent development of asthma and atopy. These results, however, should be interpreted carefully because of the small number of cases evaluated.

This study suggested that lower respiratory tract illnesses, especially those caused by RSV occurring in infancy, were associated with increased risk of subsequent wheezing during early childhood. The tendency to wheeze disappears with increasing age in many children. We also found that recurrent episodes of wheezing during the first 5 years of life and symptoms suggestive of allergic rhinoconjunctivitis were the only factors predictive of subsequent diagnosis of asthma for children who had lower respiratory tract illnesses during early childhood.

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