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Original Article

Frequency and severity of lower respiratory infections associated with persistent asthma in children: A retrospective birth cohort population-based study

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Background: The influences of frequency and severity of respiratory infections in early life on early and late asthma development have not yet been confirmed.
Materials and Methods: Data from the National Health Insurance Research Database (NHIRD) for the period 1996-2012 were used to obtain a birth cohort of children. Persistent asthma (AS) was defined as AS diagnosis before the age of two years with persistence of AS to the age of twelve years. Late-onset AS referred to first AS diagnosis after the age of five years.
Results: A total of 2,305 children were included in persistent AS group and a total of 2,834 children were included in late-onset AS group in our birth cohort study. There were significant differences in the frequencies of lower respiratory infections between the two groups, for those under 2 years of age and for those between 3 and 5 years of age (7.2± 6.1 vs 3.5±4.0 , 6.8±6.0 vs 4.9±5.0 respectively, $p<0.001$). Rates of emergency department visits due to lower respiratory infection were 24.6% in persistent AS group and 9.0% in late-onset AS group with adjusted odds ratio (OR) of 3.2 (95% confidence interval (CI): 2.7-3.7) for under 2 years of age. At 2-5 years of age, frequencies were 20.4% and and 12.0% in persistent AS and late-onset AS groups, respectively, with adjusted OR of 1.8 (95% CI:1.6-2.2). Hospitalization rates due to lower respiratory infection were 35.1% in persistent AS group and 9.6% in late-onset AS group with adjusted OR of 5.0 (95% CI:4.3-5.8) for under 2 years of age. At 2-5 years of age, these rates were 25.6% and 11.9% in peristent AS and late-onset AS groups, respectively, with adjusted OR of 2.5 (95% CI:2.2-2.9).
Conclusion: The frequency and severity of lower respiratory infections are associated with early and late asthma development.

Key words: Early-onset asthma; late-onset asthma; lower respiratory infections; persistent asthma

Introduction

Most studies support the concept that both genes and the environment contribute to the development of asthma (AS).[1]. Respiratory infection is an environmental factor. It not only produces morbidity in the short term, but also is associated with an increased risk of asthma development later in childhood.[2,3] In recent studies, AS patients have been shown to be more susceptible to rhinovirus infection than healthy individuals.[4,5] This can be explained by the upregulation of the receptor for 90% of rhinoviruses, ICAM-1, in the lower airway epithelium of individuals with AS.[6,7] From previous epidemiologic surveys, before the age

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of three years, other viral infections with lower airway involvement (e.g. parainfluenza, influenza A) are associated with chronic lower respiratory tract symptoms including AS.[8,9] Therefore, upper and lower airway infections due to viruses during infancy and early childhood play an important role in the development of AS. About 20-53% of infants present with one episode of lower respiratory tract infection in the first year of life.[10,11] Most respiratory infections in children are caused by viruses, such as rhinoviruses, RSV, parainfluenza viruses, and influenza, which are identified on culture or antigen test or by molecular laboratory techniques.[12-13]. However, sensitivities of these methods vary. For example, Shetty et al.[14] compared the sensitivities of direct fluorescent antigen with culture, and the adenovirus antigen test was shown to be only 47% sensitive.

Bacterial infections also play important roles. Bisgaard et al.[15] conducted a prospective birth cohort study and found that acute wheezy episodes in young children are significantly associated with bacterial infections. A recent double-blind, randomized, placebo-controlled clinical trial showed that telithromycin is effective in the treatment of acute exacerbations of AS in adults[16] and clarithromycin alleviates the symptom burden and reduces the risk of readmission for respiratory syncytial virus-related bronchiolitis.[17] Bacterial and atypical bacterial infections influence the development and control of AS.

How can we predict whether or not viral infections are associated with persistent AS? To answer that question, we conducted a birth cohort study to evaluate respiratory infections after birth including bacterial and viral infections associated with later AS to understand if severity of infections influences the results.

Materials and Methods

Data source

In March 1995, Taiwan developed the unique, single-payer, government-run National Health Insurance Program (NHIP). By 2007, 22.60 million of the 22.96 million residents of Taiwan were enrolled in this program.[18] The large computerized databases that became the National Health Insurance Research Database (NHIRD) were derived from this program by the Bureau of National Health Insurance. The NHIRD is maintained by the National Health Research Institutes and used for research purposes. Personal, physicians', and medical care institutions' identities are scrambled in compliance with the Personal Electronic Data Protection Law.

Data collection

Each computerized claim form in the Longitudinal Health Insurance Databases, data subsets of the NHIRD, includes patients' personal identification number (scrambled ID), age, gender, visit dates, medical care institutions, primary physicians, and diagnoses relevant to each visit. All visits (including well-baby check-ups, ambulatory visits, emergency department visits, and hospitalizations) were linked by scrambled ID from 1996 to 2012.

Subjects were selected based on the diagnosis of AS (International Classification of Diseases [ICD], Ninth Revision, Clinical Modification ICD-9-CM code 493.xx). As only a maximum of three out-patient and five in-patient diagnoses can be listed per encounter, AS cases were included in this cohort study (12 years) based on the following criteria:

1. At least three out-patient visits due to AS.
2. An emergency department visit or hospitalization in which AS was the major (first) diagnosis
3. One emergency department visit or one hospitalization for which AS was not the major diagnosis with at least two out-patient visits due to AS.

We classified the subjects into two groups. One group (persistent AS) was defined as patients diagnosed with AS before the age of 2 years with AS persisting until the age of 12 years. The other group (late-onset AS) was defined as patients with first diagnosis of AS after the age of 5 years.

Data Collection and Diagnostic Codes

A total of 45,408 children born between 1997 and 2000 were randomly selected from the NHIRD. After excluding those with incomplete

basic data, or who did not fit the criteria, a total of 5,139 children were included in this study. Their claims data from birth to 12 years of age were analyzed. A low socioeconomic status was defined as a family income of less than 1 million New Taiwan Dollars per year (in 2012, the exchange rate was New Taiwan Dollars 30.1 to US Dollar 1). Urban area was defined as a city with a population of more than 2 million. If a subject had moved from an urban to rural or a rural to urban area, the status was listed as unknown during the 12 year cohort period. Upper respiratory infections, lower respiratory infections and otitis media were defined by ICD-9-CM codes for at least one outpatient visit, inpatient admission, or emergency room visit (Table 1)

Statistical analysis

All analyses were performed using SAS version 9.2 for Windows (SAS Institute Inc., Cary, NC, USA) and SPSS 12.0 (SPSS Inc., Chicago, IL , USA). The basic demographic data were compared between the two groups using ANOVA and Student t test. The rates of upper respiratory infections, lower respiratory infections and otitis media per year are presented as mean ± standard deviation. When comparing the differences between the two groups, ANOVA was used. To evaluate the association between asthma and severity (emergency department visit and hospitalization), multiple regression was used, adjusted for sex, urban area and socioeconomic factors. Odds ratios (ORs) were determined as risk estimates, and their 95% confidence intervals (CI) were estimated. P value <0.05 indicated statistical significance.

Table 1. ***The ICD-9-CM codes used in our study***

Diagnosis	*ICD-9*
1.Otitis media	381*
	382
	384
2.Upper respiratory infection	
Acute nasopharyngitis	460
Acute sinusitis	461
Acute pharyngitis	462
Acute tonsillitis	463
Acute upper respiratory infections of multiple or unspecified sites	465
Acute laryngitis and tracheitis	464**
3.Lower respiratory infection	
Acute bronchitis and bronchiolitis	466
Pneumonia	480-486
Bronchitis, not specified as acute or chronic	490

381: not including 381.5-381.9*
*464**: not including 464.1,464.2, 464.4*

Results

In total, 2,305 children were included in the persistent AS group (boys, 64%; girls, 36%). The late-onset AS group consisted of 2,834 children (56% boys). The majority lived in urban areas (34% in persistent AS, 38% in late-onset AS) and had high socio-economic status (82-85%). Furthermore, about 43% and 44% of the families had moved in the two groups, respectively. (Table 2)

There was higher frequency of respiratory infection every year in persistent AS group than in late-onset AS group, both for those under 2 years of age and those 3-5 years of age (9.2± 8.5 vs 8.9±7.9 , 13.4±7.9 vs 13.3±8.1, respectively). The difference was not significant (p=0.2 and 0.6). However, there were significant differences in frequencies of lower respiratory infections and acute otitis media between the two groups, not only for those under 2 years of age, but also for those between 3 and 5 years of age. (p<0.001, Figure 1).

Children who had been admitted to a hospital or had emergency department visit before the age of 5 years due to lower respiratory infection were further analyzed. In the persistent AS group, there was a frequency of 24.6% of emergency department visits compared with 9.0% for late onset AS group before 2 years of age (OR 3.3). Due to the utilization of heterogeneous basic data in the two groups, we further adjusted for age, sex, city and socioeconomic status. However, the OR was still 3.2 (95% CI: 27.-3.7). The hospitalization rate was 35.1% in the persistent AS group and 9.6% in the late-onset group before the age of 2 years. Adjusted OR was 5.0 (95% CI:4.3-5.8). For children 2-5 years old, the rate of emergency department visits decreased to 20.4% in the persistent AS group, and increased to 12% in the late-onset AS group. However, adjusted OR was still 1.8 (95% CI: 1.6-2.2). The hospitalization rate in the persistent AS group decreased to 25.6%, which was higher than the hospitalization rate in the late onset AS group (increased to 11.9%) for those 2-5 years of age. Adjusted OR was 2.5 (95% CI: 2.2-2.9).

Discussion

From the results of this retrospective birth

Table 2. ***Demography of characteristics of the two groups***

	Persisted AS		*Late-onset AS*		
	Number	*%*	*Number*	*%*	*P-value*
	2305		*2834*		
Sex					<0.001
Male	*1482*	*64%*	*1584*	*56%*	
Female	*823*	*36%*	*1250*	*44%*	
City					0.002
Urban	*791*	*34%*	*1087*	*38%*	
Rural	*498*	*22%*	*521*	*18%*	
Unknown	*1016*	*44%*	*1226*	*43%*	
Socioeconomic Status					0.01
Height	*1895*	*82%*	*2402*	*85%*	
Low	*410*	*18%*	*432*	*15%*	

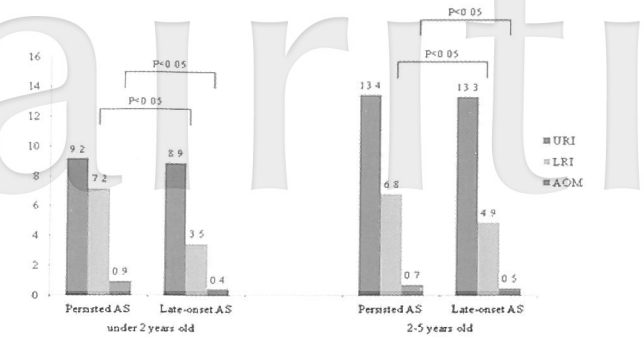

Figure.1. The average rate per year of upper respiratory tract infection (URI), lower respiratory tract infection (LRI) and acute otitis media (AOM) under 2 years old and 2-5 years old in the persistent asthma (AS) and late onset asthma (AS) group.

cohort study, in the persistent AS group, respiratory tract infection frequencies, especially for lower respiratory tract infections, were significantly higher than in the late-onset AS group for patients under 2 years of age and between 2 and 5 years of age. The persistent AS group also had higher numbers of emergency department visits and hospitalizations due to incidences of lower respiratory infections before the age of 5 years.

Whether early infection, especially respiratory tract infection, is a risk factor for the development of AS has long been a topic of discussion. From the infection source view, some viral infections (e.g., respiratory syncytial virus, rhinovirus, influenza and parainfluenza) are associated with asthma. The association between asthma and respiratory infections due to bacterial microorganisms has been indirectly proven by antibiotic prescriptions in previous studies. Moreover, previous studies have demonstrated that lower respiratory tract infections such as pneumonia are associated with an increased risk of AS.[19–22] In contrast, upper respiratory tract infections have been suggested to be associated with a reduced risk of allergic diseases.[20, 21] These previous studies focused on early respiratory infection with or without associated incidence of AS later on. In the present study, for those diagnosed with AS before the age of 2 years, the frequency of lower respiratory infection under the age of 5 years was significantly higher than in those who had been diagnosed with AS after the age of 5 years. There was no significant difference in the frequency of upper respiratory infections between the groups. Lower respiratory infections played an important role in the development of AS in early life. It is reasonable to assume that lower respiratory infection, whether caused by virus or bacteria, is a trigger factor for AS. The greater the frequency of lower respiratory infections, the earlier the development of AS.

If lower respiratory infections are severe, children may need more emergency department visits and even hospitalization. Previous studies have seldom noted the severity of lower respiratory infections. In the present study, the persistent AS group had more emergency department visits (OR: 3.3 under 2 years, 1.9 between 3-5 years) and a higher hospitalization rate (OR:5.1 and 2.6 respective age group). This means that not only the frequency of lower respiratory infections, but also the severity of infections, is a major trigger factor for AS. Our findings were in agreement with the relationship between lower respiratory infection and AS mediated by nonatopic mechanisms (e.g., increased airway inflammation and airway reactivity). An alternative explanation for the observed association is that infants with lower lung function near birth are more susceptible to lower respiratory infections such as bronchiolitis and pneumonia and might go on to develop AS later in childhood.[23]

Upper respiratory infections in early childhood might protect against atopy by stimulating maturation of the TH1 immune response, leading to a more balanced TH1/TH2 system, as opposed to the predominance of TH2 cells in infancy.[24] In our study, upper respiratory infection did not play a role in the development of AS. There were no significant differences in the frequency of upper respiratory infections among subjects under the age of 5 years. Otitis media is a common upper respiratory infection usually accompanied by the common cold. The rate of otitis media was far lower than that of upper respiratory infection, with significant differences between the two groups. A previous study also demonstrated a positive association between recurrent otitis media in the first year of life and atopy at the age of 2 years.

Table 3. ***The number of children in the persistent asthma (AS) and late-onset asthma (AS) groups that had ever been required to make an emergency visit and to be hospitalized when they were under 2 years old and between 2-5 years old.***

	Persisted AS		*Late-onset AS*					
	Number	*%*	*Number*	*%*	*OR*	*95%CI*	*ad-OR*	*95%CI*
	2305		*2834*					
Under 2 years old								
Emergency Visit	*566*	*24.6%*	*256*	*9.0%*	3.3	2.8-3.8	3.2	2.7-3.7
Hospitalization	*809*	*35.1%*	*272*	*9.6%*	5.1	4.4-6.0	5.0	4.3-5.8
Between 2-5 years old								
Emergency Visit	*470*	*20.4%*	*341*	*12.0%*	1.9	1.6-2.7	1.8	1.6-2.2
Hospitalization	*591*	*25.6%*	*336*	*11.9%*	2.6	2.2-3.0	2.5	2.2-2.9

[25] Another cross-sectional study also found that history of ear infections is positively associated with childhood AS.[26] In contrast, Ramsey et al. found that physician-diagnosed ear infections in the first year of life protect against the development of atopy in children.[27] To better understand the influence of ear infections on AS, more surveys are required.

There are two major limitations to our study. First, we could not identify the respiratory infection etiology such as viral or bacterial. Antibiotic prescriptions can only partially separate bacterial from viral infections. We emphasize that frequency and severity of lower respiratory infections are more important than etiology. Second, we did not have any laboratory examination data to help with the diagnosis of AS. It is difficult to accurately diagnosis AS in patients under 5 years of age. Most of the guidelines suggest that history is more important than laboratory test data. In addition to the large number of participants and long follow-up to age 12, the strength of our birth cohort study was the utilization of comprehensive information. This comprehensiveness was due to the longitudinal characteristics of the study design, which allowed for follow up to full development of AS in childhood. This type of data is more reliable than that obtained via questionnaires or recalling.

In conclusion, the relationship between early-life respiratory infections and asthma is complex. Respiratory infections are very common in early childhood. The frequency of upper respiratory infections is not associated with later development of AS. However, according to our study, early childhood lower respiratory infection is an important trigger factor for AS development. Furthermore, the frequency of infection under the age of 5-years and the severity of infection have great influence on AS development.

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