Recurrent wheezing after respiratory syncytial virus infection in children under 3 years of age: a 1-year follow-up study

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Abstract

Background: Wheezing in infancy is very common. RSV infection can cause recurrent wheezing. The aim of this study was to explore the risk factors of recurrent wheezing in children under 3 years of age after RSV infection.

Methods: We chose children with initial wheezing before 3 years of age who were hospitalized for medical treatment. Wheezing frequency was determined by follow-up at 1 week, 1 month, 3 months, 6 months, and 1 year. Information such as birth status, age, sex, preterm, mode of delivery, birth order, eczema history, personal allergy history, family allergy history, passive smoking, and place of residence (urban/rural) was collected. Total serum IgE level, serum allergen testing, routine blood tests, C-reactive protein level, procalcitonin level, respiratory pathogens tests, sputum culture, chest radiography or computed tomography were performed in all patients. The correlation between each factor and wheezing recurrence was evaluated.

Results: A total of 259 children were included in the study. They were divided into single recurrence, multiple recurrences, and no recurrence groups. There were significant differences between the single recurrence and multiple recurrences groups in terms of personal allergy history, passive smoking, total serum IgE level, age, hospital stay duration, and wheezing duration ($p<0.05$). The percentage of children with a personal allergy history in the multiple recurrences group was significantly higher than that of children in the single recurrence and no recurrence groups ($p=0.031$ and 0.008, respectively). The age of children in the multiple recurrences group was significantly lower than that of children in the single recurrence group ($p=0.000$). The cost of re-hospitalization in the multiple recurrences group was significantly higher than that in the single recurrence and no recurrence groups ($p=0.000$ and 0.000, respectively).

Conclusions: Children with a personal allergy history were more likely to have wheezing episodes. The frequency of wheezing in children under 3 years of age within 1 year of a respiratory syncytial virus infection was related to age. The younger the age at the time of the onset of wheezing, the more wheezing recurrences in the following year.

Background

About a third of infants experience at least 1 wheezing episode before 3 years of age, and half experience a wheezing episode by 6 years of age. However, not all infants who experience wheezing continue to wheeze. Almost a fifth of these infants suffer from recurrent wheezing in Latin American countries, indicating an important public health problem[1]. Viral infections are the most common cause of wheezing in infants and young children, with human respiratory syncytial virus (RSV) being the most common[2, 3]. RSV infection can cause irreversible lung damage and increase the incidence of chronic lung disease in adulthood[4]. Prospective epidemiologic studies of lower respiratory tract infections caused by RSV in early life have demonstrated subsequent asthma and airway hyper-responsiveness

rates 25–80% greater than in uninfected controls up to 11 years later[5, 6]. The clinical treatment of recurrent wheezing is difficult and has many influencing factors, greatly burdening families and society.

Allergen sensitization in early life is an important risk factor for the persistence of wheezing after 6 years of age, and it is positively correlated with the intensity of anaphylaxis. Other studies have shown that the incidence of wheezing may be related to multiple factors such as maternal conditions, personal fitness, and environmental factors[7, 8]. However, there are few follow-up studies on infant wheezing. In this study, children under 3 years of age were followed up for a year after an initial wheezing episode. The frequency and risk factors of recurrent wheezing were analyzed. Early intervention may reduce the incidence of recurrent wheezing and improve prognosis, which is beneficial to disease control, and it may greatly reduce future medical expenses and family burden.

Methods

Study population

We included children with an initial wheezing episode before 3 years of age who were hospitalized for medical treatment in the Maternal and Child Health Hospital in Ganzhou from January 2018 to March 2019. All children were tested for RSV infection only. We excluded those with cardiopulmonary dysplasia, gastroesophageal reflux, tuberculosis, laryngeal softening, mediastinal masses, immune deficiencies, and tracheal or bronchial foreign bodies.

Data collection

Information such as birth status, age, sex, preterm, mode of delivery, birth order, eczema history, personal allergy history, family allergy history, passive smoking, and place of residence (urban/rural) was collected. Total serum immunoglobulin E (IgE) level, serum allergen testing, routine blood tests, C-reactive protein level, procalcitonin level, testing for 11 antibodies against respiratory pathogens, nasopharyngeal aspirate testing, sputum culture, chest radiography or computed tomography, echocardiography, and color Doppler echocardiography were performed in all patients. The patients were followed up at 1 week, 1 month, 3 months, 6 months, and 1 year. In the first 3 visits, information was collected mainly through the family members of the sick child coming to the hospital. For the last 3 encounters, information was collected mainly by telephone. The follow-up information involved the duration of additional wheezing episodes, what induced the wheezing, re-hospitalization, duration of re-hospitalization, drug use, comorbidities, recurrence of wheezing, cost of re-hospitalization, etc.

Statistical analyses

Patients were divided into study group (recurrence group: single recurrence group, multiple recurrence group) and control group (no recurrence group).

SPSS 17.0 software was used for statistical analysis of clinical data. Counting data were described by cases and percentage. Categorical variables were compared by Chi-square test. F test was used for normal distribution between two groups, and non-parametric rank sum test was used for skewed

distribution. Measurement data were expressed as mean ± SD (normal distribution). Two independent sample tests were used for inter-group comparison. Non-normal distribution data were expressed as the median and inter-quartile range. When significant differences were identified, individual groups were compared using the Man-Whitney U-test. A p value of less than 0.05 was considered statistically significant.

Results

A total of 259 children were included in the study. There were 188 males and 71 females. The average age at the time of the initial wheezing episode was 8.91 ± 7.71 months. There were 152 urban residents (58.7%). The average hospital stay duration was 6.31 ± 2.43 days. Among the 259 children, 147 experienced wheezing again within 1 year, and the recurrence rate was 56.8%. Among these 147 children, 79 (30.5%) had a single recurrence and 68 (26.3%) had 2 or more recurrences.

In the single recurrence group, there were 53 males, 10 cases of premature delivery, 54 cases of natural childbirth, 45 urban residents, 11 patients with a family allergy history, and 3 patients with a personal allergy history. The average age at the time of the initial wheezing episode was 12.04 ± 8.25 months. The hospitalization duration ranged from 2 to 12 days, with an average of 6.42 ± 2.2 days. IgE levels fluctuated from 0 to 1372 IU/mL, and the average IgE level was 123.13 ± 257.61 IU/mL. The duration of wheezing fluctuated from 1 to 37 days, with an average of 5.95 ± 8.05 days.

In the multiple recurrences group, there were 55 males, 9 cases of premature delivery, 45 cases of natural childbirth, 43 urban residents, 8 patients with a family allergy history, and 9 patients with a personal allergy history. The average age at the time of the initial wheezing episode was 7.71 ± 7.03 months. The hospitalization duration ranged from 2 to 18 days, with an average of 6.71 ± 2.39 days. IgE level fluctuated from 0 to 990 IU/mL, and the average IgE level was 103.75 ± 180.17 IU/mL. The duration of wheezing fluctuated from 1 to 31 days, with an average of 6.44 ± 6.19 days.

The single recurrence and multiple recurrences groups were compared. There were no significant differences in terms of sex, place of residence, mode of delivery, premature delivery, or family allergy history between the 2 groups ($p > 0.05$). There were significant differences between the 2 groups in terms of personal allergy history, passive smoking, total serum IgE level, age, hospital stay duration, and wheezing duration ($p < 0.05$). The percentage of children with a personal allergy history in the multiple recurrences group was significantly higher than that of children in the single recurrence and no recurrence groups ($p = 0.031$ and 0.008, respectively). The age of children in the multiple recurrences group was significantly lower than that of children in the single recurrence group ($p = 0.000$). The hospitalization duration for children with initial wheezing in the multiple recurrences group was significantly longer than that for children in the single recurrence and no recurrence groups ($p = 0.042$ and 0.016, respectively). The cost of re-hospitalization in the multiple recurrences group was significantly higher than that in the single recurrence and no recurrence groups ($p = 0.000$ and 0.000, respectively). This information is presented in Table.

Table Comparison of each factor among three groups.

	[a] single recurrence group（n=79）	[b] multiple recurrences group（n=68）	[c] no recurrence group（n=112）	P
With personal allergy history	3	9	3	Pab=0.031 Pbc=0.008
With family allergy history	11	8	12	P=0.796
Birth order	1.87±0.79（1-5）	2.18±0.98（1-6）	1.96±1.03（1-8）	Pab=0.05 Pbc=0.043
Age（months）	12.04±8.25（2-36）	7.71±7.03（1-34）	7.86±5.97（1-36）	Pab=0.000 Pbc=0.000
Place of residence (urban/rural)	45	43	64	P=0.675
Preterm	10	9	14	P=0.084
Sex（man）	53	55	80	P=0.163
Mode of delivery （Spontaneous Labor）	54	45	74	P=0.94
Passive smoking	3	12	4	Pab=0.023 Pbc=0.008
Total serum IgE level（IU/ml）	123.13±257.61（0-1372）	103.75±180.17（0-990）	58.76±100.34（0-470）	Pbc=0.012
Hospital stay duration（days）	6.42±2.2（2-12）	6.71±2.39（2-18）	598±2.56（1-16）	Pab=0.042 Pbc=0.016
Wheezing duration when hospitalization（days）	5.95±8.05（1-37）	6.44±6.19（1-31）	5.1±8.33（1-66）	Pab=0.097 Pac=0.286 Pbc=0.003
Cost of re-hospitalization （yuan）	2938.65±2009.887（0-8790）	6987.14±4074.981（0-21680）	0	Pab=0.000 Pac=0.000 Pbc=0.000

[a] single recurrence group, [b] multiple recurrences, [c] no recurrence

Discussion

In recent years, there have been many reports on the correlation between RSV infection and infant wheezing. RSV is not only the main cause of early respiratory tract infection in infants, but it is also a main risk factor for infant wheezing[9]. RSV infection can cause airway inflammation and vasospasm in infants, leading to long-term airway hyper-responsiveness and recurrent wheezing. Severe RSV infection has repeatedly been associated with long-term complications, including impaired lung function, recurrent wheezing, and asthma. Because infant respiratory system development is not perfect, neither is immune system maturation, and early pathogen exposure can easily cause wheezing. The immunity acquired by RSV infection is not lasting. Bertrand suggested that interleukin (IL)-3 and IL-12p40 could be molecular predictors for recurrent wheezing due to RSV infection[10]. He presented a comprehensive cytokine and chemokine profile analysis in the upper and lower airways of infants with RSV bronchiolitis and identified key mediators directly associated with clinical outcomes within 3 years of patient follow-up. Acute bronchiolitis in infancy is considered a risk factor for recurrent wheezing in childhood. The present study assessed the prevalence of wheezing, the clinical manifestations and risk factors for recurrent wheezing during the first 3 years of life, and persistent wheezing beyond this age in children hospitalized as young infants with acute bronchiolitis. Hospitalization for acute bronchiolitis within the first 6 months of life is an independent risk factor for recurrent wheezing during the first 3 years of life[11]. Hosoki conducted a study of 99 Japanese patients with RSV-associated hospitalizations using questionnaires and follow-up surveys. He found that age on admission, atopic profile, history of continuous nocturnal cough before

admission, gestational age, birth weight, hospital stay duration, perinatal abnormality, environmental tobacco smoke, parental allergy and asthma history, presence of siblings, and sibling allergy and asthma history were not associated with subsequent wheezing[12].

This study showed that infants with allergic constitution had a higher probability of frequent wheezing than infants with non-allergic constitution. Atopic constitution and infant wheezing have certain correlation. Allergenic sensitization is a main cause of wheezing[13]. RSV infection prevalence, eosinophil percentage, and serum eosinophil-derived neurotoxin levels are the predominant risk factors of wheezing and could therefore be used to predict recurrent wheezing in infants[14]. The risk factors for developing asthma by 6 years of age in children hospitalized for wheezing before 2 years of age are eosinophils in the blood, atopic dermatitis, elevated serum IgE levels and wheezing onset in early life. It has been suggested that the defining factor of childhood asthma is atopy[8]. A viral infection may aggravate an allergic reaction in some cases[15]. Martinez suggested that transient wheezing in young children is not associated with an atopic predisposition[16].

This study found that the recurrence of wheezing was related to age. The younger the age at the time of the initial wheezing episode, the more wheezing recurrences in the following year. Infants with RSV infection have a significantly higher risk of wheezing in the following year than those infected with other pathogens, and targeted antiviral therapy, especially in younger children, may reduce the risk of recurrent wheezing[17]. Matricardi showed that the incidence of wheezing declined with age[18]. Guo found that the number of wheezing episodes decreased significantly during the follow-up stage and that the age at the onset of wheezing was earlier in those with transient wheezing than in those with persistent wheezing[19]. The respiratory system gradually undergoes development with age, which may be an important reason for the decrease in the number of wheezing episodes[20].

Conclusions

This study found that personal allergy history and age were predictive of wheezing in infants within the year following an initial RSV infection, which helps to identify and predict the risk of recurrent wheezing in infants. Early intervention is available for infants and young children at high risk of recurrence. This study included a relatively small number of children, and the children were from a unit of our hospital; thus, there may be some case-selective bias. A multicenter prospective clinical study should be performed to further evaluate the risk factors of recurrent wheezing in infants and young children; this would provide more sufficient clinical evidence for the diagnosis, treatment, and prevention of recurrent wheezing in infants. In addition, because this study is a retrospective survey, bias in the collection of information due to memory bias is inevitable. Further, we were unable to assess patients' pulmonary function at the time of follow-up. We will therefore continue to follow them up and assess their lung function and changes in allergens that may be allergenic. Nevertheless, the results of this study still have high reference value for the management and prevention of infant wheezing.

List Of Abbreviations

Respiratory syncytial virus (RSV); Immunoglobulin E (IgE); Interleukin (IL)

Declarations

Competing interests

The authors have no conflict of interest to declare.

Authors' contributions

L Z and J R contributed to the concept and design of the study, analyzed and interpreted the data, and assisted in the critical writing. J L and F H helped to analysis statistic. L Z and H X contributed to the collection of clinical information. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics and Research Council of Women and Children's hospital of Ganzhou, and signed consent was obtained from each child's parents or foster parents.

Consent for publication

All authors have read and approved the content, and agree to submit it for consideration for publication.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

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