RESEARCH STUDIES

Investigation of factors facilitating recurrent wheezing in infants

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Abstract

Background: The purpose of the present study was to investigate the influence of particular factors on the development of wheezing during hospital treatment of acute respiratory infections (ARI) and recurrent wheezing following discharge.

Material and methods: Are followed 117 infants hospitalized because of ARI during 12-18 months after discharge. Infants underwent hospital treatment inside the time period from 2009 to 2011 years. The age of the infants at the time of hospitalization was in the range of 9 days – 11 months, 103 of them were not older than 6 months of age. 76 infants were boys and 41 were girls. These children were tested for the presence of RSV antigen in nasopharyngeal discharge using immunochromatographic assay described elsewhere. Nasopharyngeal smears were taken during the first 3 days of ARI. The role of different factors in the development of acute wheezing during hospital treatment as well as recurrent wheezing was tested by means of logistic regression. The frequency of episodes as function of particular factors was studied by means of multiple regression. After admission to the hospital children were tested for the presence of respiratory syncytial virus (RSV) antigen in nasopharyngeal discharge.

Results: Pneumonia was diagnosed in 49 of them, bronchitis – in 58, bronchiolitis – in 2 infants. In 2 infants bronchitis was accompanied with otitis media. In 28 infants the pneumonia and in 45 infants bronchitis were accompanied with wheezing. Vast majority received hospital treatment up to 15 days and less. The factors that influence wheezing during ARI are the presence of RSV antigen in nasopharyngeal smears and age at the time of admission. The factors that independently influence the development of recurrent wheezing after discharge from the hospital are smoking in accommodation and average time interval (in months) during which one episode of ARI was observed as well as the age of the baby at the time of admission.

Conclusions: RSV infection and older age of infants enhanced the development of wheezing during hospital treatment of ARI. Smoking in accommodation, frequent ARI episodes and older age at the time of admission enhanced recurrent wheezing after the discharge from the hospital. Allergic father and congenital heart malformation increased the frequency of recurrent wheezing episodes.

Key words: respiratory syncytial virus (RSV), wheezing, infants, bronchiolitis.

Introduction

Causal relationship between different factors including acute respiratory infections and wheezing as well as subsequent asthma is widely discussed in the literature. Two viruses, namely: respiratory syncytial virus (RSV) and human rhinovirus (HRV) were identified as being associated with wheezing. RSV infection in infants may cause severe course of acute respiratory infections (ARI). RSV bronchiolitis and pneumonia are common [1]. RSV facilitates bronchial obstruction and wheezing during acute phase of infection. At the same time the correlation between RSV and recurrent wheezing and bronchial asthma is less evident and remains questionable. Important role of allergic sensitization and allergic predisposition has been recognized [2]. Preventing of severe RSV bronchiolitis is believed to be able to reduce the development of recurrent wheezing illnesses [3]. However there are conflicting results and conclusions concerning the role of RSV infection in development of recurrent wheezing and asthma.

The purpose of the present study was to investigate the influence of particular factors on the development of wheezing during hospital treatment of acute respiratory infections and recurrent wheezing following discharge from the hospital.

Material and methods

We followed 117 infants hospitalized because of ARI to the Lviv City Children's Clinical Hospital during 12-18 months after discharge. Infants underwent hospital treatment inside the time period from 2009 to 2011 years. The age of the infants at the time of hospitalization was in the range of 9 days – 11 months, 103 of them were not older than 6 months of age. Gestational age varied from 25 to 41 weeks. 76 infants were boys and 41 were girls. Pneumonia was diagnosed in 49 of them, bronchitis – in 58, bronchiolitis – in 2 infants. In 2 infants bronchitis was accompanied with otitis media. In 28 infants pneumonia and in 45 infants bronchitis were accompanied with wheezing. Vast majority received hospital treatment up to 15 days and less.

These children were tested for the presence of RSV antigen in nasopharyngeal discharge using immunochromatographic assay described elsewhere [4]. Nasopharyngeal smears were taken during the first 3 days of ARI.

The role of different factors in the development of acute wheezing during hospital treatment (including mild wheezing in the bronchiolitis cases) as well as recurrent wheezing was tested by means of logistic regression. The frequency of episodes as function of particular factors was studied by means of multiple regression. The factors tested for the possible influence on the development on wheezing were following (tab. 1).

Table 1

Testing factors for their responsibility for wheezing

Factors that may be responsible for wheezing during hospital treatment of ARI	Factors that may be responsible for recurrent wheezing after discharge
Age	Age
Gestational age	Gestational age
Presence of RSV	Presence of RSV
Diagnosis	Diagnosis
X-ray diagnosis	X-ray diagnosis
Leukocytosis and differential white cells count	Leukocytosis and differential white cells count
C-reactive protein	C-reactive protein
Birth weight	Birth weight
Antibiotics during first week of life	Antibiotics during first week of life
Breastfeeding or formula feeding	Breastfeeding or formula feeding
Parity	The number of months of breastfeeding
The number of children in the family	Duration of intensive care
Symptoms of allergy prior to ARI	Days of Ventolin administration
Allergy in mother	Days of aminophylline administration
Allergy in father	Age of solid food introduction
Allergy in siblings	Parity
Presence of a congenital heart malformation	The number of children in the family
	Symptoms of allergy prior to ARI
	Allergy in mother
	Allergy in father
	Allergy in siblings
	Smoking in the environment
	ARIs after discharge
	Presence of a congenital heart malformation

Information concerning presence of the factors listed in table 1 were obtained from patients' examination, hospital case medical documentation, outpatients' personal medical documentation, interview with parents and attending physicians. Data of 19 children after discharge were incomplete, so episodes of recurrent wheezing were evaluated in 98 children out of 117 ones.

Results

The duration of hospital treatment of infants with ARI varied from 2 to 47 days (tab. 2).

Table 2

Duration of hospital treatment

Duration, days	RSV+	RSV+, %	RSV -	RSV -, %
< 10 days	13	35.14	33	41.25
10-15 days	21	56.76	37	46.25
> 15 days	2	5.40	5	6.25
> 20 days	1	2.70	5	6.25
All	37	100	80	100

Out of 117 infants 37 appeared to be RSV-positive and 80 – RSV-negative. Wheezing was observed in 75 infants, in 32 RSV-positive and 45 RSV-negative ones. After discharge from the hospital recurrent wheezing was observed in 16 children.

By means of logistic regression were defined the factors that independently influence the development of wheezing during the hospital treatment of ARI as well as during one year follow up after discharge from the hospital. The factors that influence wheezing during ARI are the presence of RSV antigen in nasopharyngeal smears and age at the time of admission (tab. 3).

Table 3

Coefficients of regression equation reflecting the probability of the development of wheezing during the hospital treatment of ARI

Variable	Coefficient	Std. Error	P
RSV-positive	2.1310	0.5634	0.0002
Age, months	0.4219	0.1248	0.0007
Constant	-0.9231		

So, the logistic regression equation is as follows:

Logit (p) of wheezing = -0.9231+2.1310 (if RSV positive) +0.4219 (age, months),

where probability (p) of wheezing = $1 : (1+e^{-logit(p)})$.

Significance level of the overall model fit $p < 0.0001$.

The factors that independently influence development of recurrent wheezing after discharge from the hospital are smoking in accommodation and average time interval (in months) during which one episode of ARI was observed and age of the baby at the time of admission (tab. 4).

Table 4

Coefficients of regression equation reflecting the probability of the development of recurrent wheezing after discharge from the hospital

Variable	Coefficient	Std. Error	P
Smoking in accomodation	2.7264	1.2638	0.0310
Time interval between ARI episodes	-0.4803	0.1773	0.0068
Age at admission, months	0.3809	0.1501	0.0112
Constant	-0.7975		

The logistic regression equation can be expressed as

Logit (p) of recurrent wheezing = -0.7975+2.7264 (if smoking in accomodation)-0.4803 x (average time interval between ARI, mo) +0.3809 x (age at admission, mo),

where probability (p) of recurrent wheezing = $1 : (1+e^{-logit(p)})$.

The significance level of the overall model fit $p < 0.0001$.

We also evaluated the influence of particular factors on the frequency of episodes of recurrent wheezing (RW) by means of multiple regression (tab. 5).

Table 5

Coefficients of the regression equation reflecting the number of episodes of recurrent wheezing per year

Independent variables	Coefficient	Std. Error	t	P
(Constant)	0.4848			
Allergic father	24.7307	3.2798	7.540	<
Congenital malformation of the heart	4.5691	2.1124	2.163	

Thus the multiple regression equation presents itself like

The number of episodes of RW/year = 0.4848+24.7307 (if allergic father) +4.5691 (if congenital malformation of the heart is present)

The significance level of the model fit $p < 0.001$.

Discussion

Thereby the results of statistics assay revealed that independent variables which facilitated wheezing during acute phase of respiratory infection were presence of RSV infection and patient's age. Variables that facilitated recurrent wheezing after discharge from the hospital were elders' smoking inside infant's inhabitation, short interval between subsequent episodes of intercurrent ARIs and age at the time of admission. The factors that independently increased the number of episodes of recurrent wheezing appeared to be the presence of allergic disease in the father as well as the presence of congenital heart malformation. Obtained data show that wheezing syndrome depends on different mechanisms and factors. In Ukraine wheezing is usually called bronchoobstruction or bronchoobstructive syndrome. This entity includes bronchiolitis, obstructive bronchitis, as well as pneumonia accompanied with obstructive bronchitis. Our study shows that acute RSV infections as well as infant's age facilitate wheezing. The elder infant (within first year of age) the more prone it is towards wheezing. It is well known that RSV often is the causal agent of bronchiolitis and pneumonia in infants. Therefore we tested presence of RSV in the upper airways of our patients. Less obvious is the influence of RSV infection on subsequent development of recurrent wheezing and asthma. Our data demonstrated that smoking inside patient's inhabitation, frequent ARI and patient's age at the time of admission to the hospital influenced independently the development of recurrent wheezing. Smoking indoors had a strong facilitating effect on recurrent wheezing. Again older age at the time of admission to the hospital favored recurrent wheezing. At the same time father's allergy and congenital heart malformation increased frequency of wheezing episodes following discharge from the hospital.

The role of RSV in inducing recurrent wheezing and asthma is widely discussed in the literature. Takeyama A. et al [5] showed that RSV as well as rhinovirus respiratory tract infection are factors in the development and exacerbation of wheezing at the time of and after virus-induced lower respiratory tract infection in patients younger than 3 years of age. At the same time rhinoviruses but not RSV appeared to be associated with subsequent recurrent wheezing and the development of asthma. L. B. Bacharier et al [6], on the contrary, demonstrated that approximately 50% of children after severe RSV bronchiolitis developed physician-diagnosed asthma before the seventh birthday. According to Sly PD, Kusel M and Holt PG [7] acute viral lower respiratory tract infections, especially those caused by RSV and rhinoviruses, are associated with asthma in later childhood via wheezing. Wheeze in early life however is not specific for subsequent asthma. Allergic sensitizations in early life as well as severe course of lower respiratory tract infection enhance the development of asthma [8, 9]. Palivizumab prophylaxis of RSV infection administered to preterm infants 33 to 35 weeks' gestational age was associated with a lower incidence of recurrent wheezing during the first 3 years of life [8].

Our study revealed that father's allergy was the factor which makes for higher frequency of recurrent wheezing episodes. This is rather unexpected result because there are studies suggesting that it is mother's atopy enhancing recurrent wheezing. Having a mother with atopic asthma was associated with more severe course of rhinovirus infection in infant. These infants with rhinovirus were more likely to have subsequent increased asthma risk [10].

The study of A. Schuurhof et al [11] revealed that local IL-10 production during RSV infection was higher in infants that later developed physician diagnosed post-bronchiolitis wheeze during the first year after RSV infection ($p = 0.02$).

Our study failed to find a relationship between RSV ARI and recurrent wheezing. This may be explained at least partially with that circumstance that RSV infected infants in our study included not only patients with bronchiolitis but also with pneumonia and bronchitis without wheezing as well. The patients were followed within one year which is relatively short period although recurrent wheezing can be detected througth this time interval. Nevertheless smoking in the apartment appeared to have the strongest influence on the development of recurrent wheezing. Higher frequency of episodes of ARI and older age of patients at the time of admission to the hospital enhanced the recurrent wheeze as well.

Conclusions

1. RSV infection and older age of infants enhanced the development of wheezing during hospital treatment of ARI.

2. Smoking in accommodation, frequent ARI episodes and older age enhanced recurrent wheezing after the discharge from the hospital.

3. Allergic father and congenital heart malformation increased the frequency of recurrent wheezing episodes.

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