

Original Article

Wheezing due to rhinovirus infection in infancy: Bronchial hyperresponsiveness at school age

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Abstract *Background:* Characteristics related to decreased lung function and increased bronchial responsiveness after early childhood wheezing requiring hospitalization are not fully established.

Methods: Seventy-nine children with wheezing requiring hospitalization at age <2 years were prospectively followed up and re-investigated at age 5.6–8.8 years when the measurements of baseline lung function and bronchial responsiveness to exercise were performed.

Results: At early school age, 23% of children had decreased lung function, and 13% had increased bronchial responsiveness to exercise. Predictors of decreased lung function were maternal history of smoking during pregnancy (odds ratio [OR], 12.8; 95% confidence interval [CI]: 1.2–139.6), parental history of asthma (OR, 4.3; 95%CI: 1.1–17.1), and female gender (OR, 4.0; 95%CI: 1.2–13.7). Increased bronchial responsiveness was associated with rhinovirus infection-induced wheezing in infancy (OR, 6.5; 95%CI: 1.2–36.3), and early cat or dog exposure leading to sensitization (OR, 26.6; 95%CI: 1.3–525.2). Inhaled anti-inflammatory therapy was common in children with rhinovirus infection-induced wheezing in infancy ($n = 13/19$; $P = 0.001$ vs children with other/no confirmed virus infection etiology for wheezing in infancy, $n = 16/60$), which may have improved lung function and attenuated bronchial responsiveness in them.

Conclusions: After early childhood wheezing requiring hospitalization, one-fourth of children will have decreased lung function and one-eighth of children will show increased bronchial responsiveness at school age. Gender, heredity of asthma, and antenatal exposure to tobacco smoke are predictors of decreased lung function, whereas rhinovirus infection etiology of wheeze and early animal exposure leading to sensitization are associated with increased bronchial responsiveness later in childhood.

Key words bronchial hyperreactivity, infant, lung function tests, rhinovirus, wheezing.

One to three percent of all infants require hospital admission for wheezing,^{1,2} and these children are especially at risk for subsequent asthma and abnormalities in lung function.^{3–8} But the early childhood characteristics related to decreased lung function and increased bronchial responsiveness later in childhood are not fully established.

In the present follow-up study a cohort of wheezy hospitalized infants were prospectively followed up to school age, and, as previously reported, it was found that several characteristics present in infancy were associated with the development of clinical asthma. These characteristics included atopic dermatitis,⁹ a history of physician-confirmed wheeze,⁹ elevated total serum immunoglobulin E (IgE),⁹ blood eosinophilia,⁹ early sensitization to inhalant allergens,¹⁰ and the rhinovirus infection etiology of wheeze.¹¹ The aim of the present study was to evaluate lung function and bronchial responsiveness with special attention to these early childhood characteristics in the same study cohort at age 5–8 years.

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Methods

Study subjects

One hundred children, aged 1–23 months, were admitted to hospital due to respiratory infection-related wheezing in 1992–1993, as described earlier in detail.¹²

Eighty-two of these children were prospectively followed up to the median age of 7.2 years (range 5.6–8.8 years), when the children were examined clinically, and the baseline lung function was measured by flow-volume spirometry (FVS), and an exercise challenge test was performed.⁹ Seventy-nine of the 82 children were capable of performing baseline lung function and exercise challenge tests, and these 79 children comprise the subjects of the present study.

Studies for viral etiology of wheezing

On admission the viral studies for respiratory syncytial virus (RSV) and six other respiratory viruses were performed on antigen detection in nasopharyngeal aspirates (NPA) and complement fixing antibody assays in paired sera.¹³ In 2000 there were frozen NPA obtained on admission available for 81 children. Supplementary viral studies were done using reverse-transcription–polymerase chain reaction (RT-PCR) for rhinoviruses, enteroviruses and

coronaviruses.¹¹ Furthermore, in 2002, detection of RSV genome on in-house RT-PCR of the F (fusion) protein gene was done in frozen NPA (obtained on admission) available for 61 children.¹⁴

Lung function testing

The baseline lung function was examined using flow-volume spirometer (Medikro, Kuopio, Finland). First, the children were carefully instructed on how to perform the test. Thereafter the measurements were repeated at least three times, and accepted if the printed graphic curves were appropriate and equal in shape. The measurement with the highest forced expiratory flow in 1 s (FEV₁) was chosen for later comparisons, as published earlier.⁹ Baseline lung function parameters were expressed as percentages of the height-related reference values (% of predicted) for Finnish children.¹⁵ The parameters measured were, functional vital capacity (FVC), FEV₁, FEV₁/FVC, and the forced expiratory flow at 50% of the FVC (FEF_{50%}). The lower limits of normality were defined as 80% for FEV₁, 88% for FEV₁/FVC, and 62% for FEF_{50%}.¹⁶

All infants were studied when they were free from current signs of respiratory infection. β -2-Agonists were withheld for 12 h prior to lung function and challenge tests.

Exercise challenge test

The baseline lung function testing was followed by exercise that consisted of free running outdoors for 8 min at a heart rate \geq 80% of the predicted maximum. The heart rate was monitored on telemetry (Polar Sport Tester, Polar Elektro, Kempele, Finland) at 1 min intervals. FVS was performed 10 min after the exercise. FEV₁ changes were calculated as follows: $[1 - (\text{FEV}_{1 \text{ post-challenge}} / \text{FEV}_{1 \text{ baseline}})] \times 100\%$. Bronchial responsiveness to exercise was evaluated using two cut-offs for increased bronchial responsiveness: a fall of \geq 12%,¹⁷ and a fall of \geq 15%¹⁸ in FEV₁ after the exercise.

Ongoing inhaled anti-inflammatory therapy

When a child was on a continuous inhaled anti-inflammatory therapy (either cromones or inhaled steroids) for asthma, the medication had been started on a clinical basis by a pediatric allergist, independently of the authors. As a probable confounding factor, the ongoing inhaled anti-inflammatory therapy was taken into account in the analyses.

Statistics

The data were analyzed using SPSS 13.0 (SPSS, Chicago, IL, USA). Statistical significance of the differences between the groups was assessed using χ^2 test for proportions. Fisher's exact test was used when the expected frequency for any cell was $<$ 5. Continuous data were analyzed using the Mann-Whitney *U*-test. Multivariate analyses were performed using logistic regression. Two-tailed tests were used in all analyses. Statistical significance was set at $P < 0.05$.

Ethics

The study was approved by the Research Ethics Committee of Kuopio University Hospital. Informed written consent was obtained from the parents of the children.

Results

Baseline characteristics

Baseline characteristics of the study children have been presented earlier in detail.^{9–11,14}

In brief: 58 (73%) of the 79 children were boys, and 47 (59%) were aged $<$ 12 months at the index episode of wheezing requiring hospitalization. The episode of wheezing was the first one in 68 children (86%); 11 children (14%) had a history of one previous episode of wheezing confirmed by a physician. Fourteen children (18%) had a parental history of asthma, 38 children (48%) had an exposure to environmental tobacco smoke, including 19 children (24%) with a maternal history of smoking during pregnancy; and 23 children (29%) had atopic dermatitis in infancy. In addition, 23 children (29%) were exposed to furry animals (i.e. cat and/or dog at home or at day care) in infancy, and the early animal exposure led to sensitization (i.e. skin prick test positivity to the animal in question by school age) in four cases and to tolerance in 19 cases. At the index hospitalization for wheezing in infancy, 16 (29%) had elevated total serum IgE (\geq 60 kU/L), and 25 children (32%) had eosinophilia (\geq 0.45 \times 10⁹ cells/L). During the index hospitalization for wheezing in infancy, sole RSV finding was detected in 16 children (20%), sole rhinoviral finding in 19 children (24%), and other single viral findings in 12 children (15%). Mixed viral findings accounted for 11 children (14%), including six cases of RSV and five cases of rhinovirus. No viruses were detected in 21 children (27%).

Lung function, and bronchial responsiveness to exercise

In the majority of children the baseline lung function was normal and bronchial responsiveness to exercise was within normal limits at school age (Table 1). But the ranges were wide, especially the range of FEF_{50%}. Eighteen children (23%) were regarded as having decreased lung function, because they had subnormal values in at least one of the three parameters of FVS, and 10

Table 1 Baseline lung function and responsiveness to exercise

	All children (n = 79) (median [range])
Baseline lung function parameters of FVS [†] (%)	
FVC	103 (71–149)
FEV ₁	98 (66–135)
<80%, n (%)	4 (5)
FEV ₁ /FVC	97 (76–115)
<88%, n (%)	13 (16)
FEF _{50%}	88 (40–126)
<62%, n (%)	14 (18)
Any subnormal FVS parameters [‡] , n (%)	18 (23)
Responsiveness to exercise (%)	
Fall in FEV ₁ [§]	2 (0–28)
\geq 12%, n (%)	10 (13)
\geq 15%, n (%)	5 (6)

[†]% of the height-related predicted value; [‡]FEV₁ $<$ 80% or FEV₁/FVC $<$ 88% or FEF_{50%} $<$ 62% of the predicted value; [§]10 min after the exercise.

FEF_{50%}, forced expiratory flow at 50% of the FVC; FEV₁, forced expiratory flow in 1 s; FVC, functional vital capacity; FVS, flow-volume spirometry.

Table 2 Predictive factors for decreased lung function ($n = 79$)

Outcome	Significant predictors of decreased lung function	No. children with the outcome	OR (95%CI) [†]
FEV ₁ < 80% ($n = 4$) [‡]	Maternal smoking during pregnancy ($n = 19$)	3	12.8 (1.2–139.6)
FEV ₁ /FVC < 88% ($n = 13$) [‡]	Parental history of asthma ($n = 14$)	5	4.3 (1.1–17.1)
FEF _{50%} < 62% ($n = 14$) [‡]	Female gender ($n = 21$)	7	4.0 (1.2–13.7)
Any subnormal lung function parameters ($n = 18$) [§]	Parental history of asthma ($n = 14$)	7	4.4 (1.3–15.4)

[†]Odds ratio adjusted for age (<12 months or ≥12 months on entry to the study) and gender; [‡]% of the height-related predicted value; [§]FEV₁<80% or FEV₁/FVC <88% or FEF_{50%} < 62% of the predicted value.

CI, confidence interval; FEF_{50%}, forced expiratory flow at 50% of the FVC; FEV₁, forced expiratory flow in 1 s; FVC, functional vital capacity; FVS, flow-volume spirometry; OR, odds ratio.

children (13%) were regarded as having increased bronchial responsiveness to exercise, because they had a fall of ≥12% in FEV₁ after exercise.

Predictive factors for decreased lung function and increased bronchial responsiveness to exercise

Predictors of decreased lung function included maternal history of smoking during pregnancy, parental history of asthma, and female gender (Table 2). Increased bronchial responsiveness was associated with rhinovirus infection-induced wheezing in infancy and early exposure to furry animals leading to sensitization (Table 3).

Influence of inhaled anti-inflammatory therapy

Twenty-nine children (37%) were on inhaled steroids ($n = 12$) or cromones ($n = 17$), and 13 (45%) of them had wheezed due to rhinovirus infection in infancy ($P = 0.001$). Of the 29 children on inhaled anti-inflammatory therapy, nine (31%) had decreased lung function and four (14%) had increased bronchial responsiveness to exercise. In all, either need for continuous medication, decreased lung function, or increased bronchial responsiveness to exercise were present in 42 children (53%). As seen in Table 4, children with normal lung function or bronchial responsiveness to exercise within normal limits at school age, were on a continuous inhaled anti-inflammatory therapy more frequently when history of rhinovirus infection-induced wheezing in infancy was

present, than those with other/no confirmed virus infection etiology for infantile wheeze.

Discussion

The present study of 79 children hospitalized for wheezing in infancy shows that 23% had reduced lung function (according to the criterion of one subnormal result out of three parameters) 5–7 years later. Increased bronchial responsiveness to exercise was present in 13% of children. Heredity of asthma, female gender, and *in utero* exposure to tobacco smoke predicted subnormal lung function parameters; and rhinovirus infection-induced wheeze in infancy and early animal exposure leading to sensitization predicted increased bronchial responsiveness to exercise at school age. In addition, especially among children with rhinovirus infection etiology for wheezing in infancy, there were more asthma patients on a continuous inhaled anti-inflammatory therapy, which may have improved lung function¹⁹ and attenuated bronchial responsiveness.²⁰

Several studies have confirmed that pulmonary function is reduced, and bronchial responsiveness is increased years after hospital admission for wheezing in infancy.^{4–6,8,21,22} In the present study lung function was decreased in 23% of children. In line with earlier publications,^{23,24} the heredity of asthma, and maternal antenatal smoking were significant predictors of subnormal lung function parameters. In addition, female gender presented a

Table 3 Early-life predictors of increased bronchial responsiveness to exercise ($n = 79$)

Outcome	Significant early-life predictors of increased bronchial responsiveness	No. children with the outcome	OR (95%CI) [†]
Fall in FEV ₁ ≥12% ($n = 10$)	Rhinovirus infection-induced wheezing ($n = 19$)	5	6.5 (1.2–36.3)
	Early exposure to cat/dog [‡]		
	Leading to sensitization ($n = 4$) [§]	2	26.6 (1.3–525.2) [¶]
Fall in FEV ₁ ≥15% ($n = 5$)	Leading to tolerance ($n = 19$) ^{††}	4	3.9 (0.7–20.0) [¶]
	Rhinovirus infection-induced wheezing ($n = 19$)	4	18.5 (1.7–199.1)

[†]Odds ratio adjusted for age (<12 months or ≥12 months on entry to the study), gender, and the significant early-life predictors of increased bronchial responsiveness; [‡]cat and/or dog at home or at day care in infancy; [§]skin prick test positivity (wheal size ≥3 mm) to the animal in question (cat/dog) by school age; [¶]compared to children with no exposure to cat/dog in infancy; ^{††}skin prick test negativity (wheal size <3 mm) to the animal in question (cat/dog) at school age.

CI, confidence interval; FEV₁, forced expiratory flow in 1 s; OR, odds ratio.

Table 4 Lung function and responsiveness to exercise versus ongoing anti-therapy ($n = 79$)

		Viral findings related to infantile wheezing		<i>P</i>
		Rhinovirus only ($n = 19$) n (%)	Other/No virus ($n = 60$) n (%)	
Decreased lung function [†]				
Anti-inflammatory therapy [‡]	No	1 (5)	8 (13)	0.294
	Yes	4 (21)	5 (8)	
Normal lung function [§]				
Anti-inflammatory therapy [‡]	No	5 (26)	36 (60)	0.008
	Yes	9 (47)	11 (18)	
Fall in FEV ₁ \geq 12% after exercise				
Anti-inflammatory therapy [‡]	No	1 (5)	5 (8)	0.027
	Yes	4 (21)	0 (0)	
Fall in FEV ₁ <12% after exercise				
Anti-inflammatory therapy [‡]	No	5 (26)	39 (65)	0.014
	Yes	9 (47)	16 (27)	

[†]FEV₁ <80% or FEV₁/FVC <88% or FEF_{50%} <62% of the predicted value; [‡]ongoing inhaled steroid or cromone therapy; [§]FEV₁ \geq 80% and FEV₁/FVC \geq 88% and FEF_{50%} \geq 62% of the predicted value.

FEV₁, forced expiratory flow in 1 s.

risk factor for subnormal FEF_{50%} at school age; although male gender is known to be associated with early childhood wheezing illnesses,²⁵ female subjects are at risk for asthma and impaired lung function later.²⁶

In the present study, bronchial responsiveness to exercise was found to be increased at school age in 13% of the children with wheezing requiring hospitalization in infancy, which is consistent with earlier findings.^{3,5,6} Early exposure to furry animals leading to sensitization was found to be associated with increased bronchial responsiveness at school age. That is consistent with current literature stressing the role of sensitization to inhalant allergens as a predictor of persistent wheezing.^{27,28} In addition, rhinovirus infection-induced wheezing in infancy was associated with increased bronchial responsiveness at school age. Such a finding is unique, because the role of viruses other than RSV on later lung function and bronchial responsiveness is poorly studied. We found three studies comparing outcomes of RSV-positive and RSV-negative infants with bronchiolitis: in these studies no differences in lung function or airway responsiveness were found at the age of 7 years^{5,22} or later.²⁹ The authors did not specify the viral etiology of wheeze in RSV-negative children, and the role of rhinoviruses, for instance, remained open. Rhinoviruses, however, are commonly encountered in wheezing children in early childhood,²⁸ and often precipitate asthma symptoms in school children.³⁰ In addition, studies on experimental rhinovirus infections in adults have reported increased airway responsiveness in allergic subjects compared with non-allergic ones,³¹ and significantly reduced FEV₁ in home recordings by patients with mild atopic asthma.³² We could not find, however, any previous follow-up studies on lung function and/or bronchial responsiveness after rhinovirus infection-induced wheezing in infancy.

Furthermore, the children with rhinovirus infection-induced wheezing in infancy were, at school age, more often on a continuous inhaled anti-inflammatory therapy than those with other/no virus infection etiology for wheeze in infancy. Prob-

ably, more children with rhinovirus infection-induced wheezing in infancy could have shown increased bronchial responsiveness to exercise if investigations were performed when free of medication.

The strengths of the present study were the long prospective follow up, from infancy to 5.6–8.8 years of age, the detailed baseline data collected on entry to the study, and the wide array of virological studies performed in the specimens obtained during the index hospitalization for wheezing in infancy. In addition, the influence of inhaled anti-inflammatory therapy on lung function and bronchial responsiveness was also evaluated.

One of the weaknesses of the study was that some of the viral studies were done using frozen samples years after the beginning of the follow up and, consequently, adequate amounts of NPA for further viral studies were not available for all children. This resulted in a small number of cases with different viral findings, and thus increased the risk for type II error in interpretation of the results. Another weakness of the study was that FVS was performed only once after the exercise, and that bronchial responsiveness was evaluated only on exercise challenge test. But FVS, when the adequacy of flow-volume curve can be checked, gives more reliable information than peak expiratory flow and pocket-sized FEV₁ meters. In addition, the exercise challenge test is commonly used, easy to perform, and mimics the everyday activities of children. We also evaluated the results of the exercise challenge on two commonly used cut-off limits for FEV₁.

In conclusion, after early childhood wheezing requiring hospital admission, one-fourth of children will have decreased lung function and one-eighth of children will show increased bronchial responsiveness at school age. Gender, heredity of asthma, and antenatal exposure to tobacco smoke are predictors of decreased lung function, whereas rhinovirus infection etiology of wheeze, and early animal exposure leading to sensitization are associated with increased bronchial responsiveness later in childhood.

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