

Wheezing requiring hospitalization in early childhood: Predictive factors for asthma in a six-year follow-up

Kotaniemi-Syrjänen A, Reijonen TM, Korhonen K, Korppi M.
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Pediatr Allergy Immunol 2002; 13: 418–425. © 2002 Blackwell Munksgaard

Although asthma is common after wheezing in early childhood, the risk factors for and the prevention of later asthma are poorly understood. During the present follow-up study, a range of possible predictive factors for school-age asthma was evaluated. The study group consisted of 82 children hospitalized for wheezing at age < 2 years in 1992–93. The baseline data were collected on entry to the study. In 1999, the children were re-examined at the median age of 7.2 years. A structured questionnaire was applied to chart the symptoms suggestive of asthma, and the children were examined clinically. An exercise challenge test, as well as skin prick tests (SPT) to common inhalant allergens, was performed. Asthma was present in 33 (40%) children, 30 (91%) having continuous medication for asthma. The significant asthma-predictive factors, present on entry to the study, were blood eosinophilia ($p = 0.0008$), atopic dermatitis ($p = 0.0089$), elevated total serum immunoglobulin E (IgE) ($p = 0.0452$), and a history of earlier episodes of wheezing in infancy ($p = 0.0468$). SPT positivity in early childhood was also associated with school-age asthma ($p = 0.002$). In contrast, respiratory syncytial virus (RSV) identification during the index episode of wheezing played a minor role as a predictive factor for asthma. In conclusion, if hospitalization for wheezing occurs in infancy, more than every third child will suffer from asthma at early school age; the risk is significantly increased with recurrent wheezing in infancy and the development of allergic manifestations.

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Key words: asthma; atopy; child; sensitization;
wheezing

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Accepted 4 March 2002

Wheezing is common in infancy; 20% of all children suffer from early childhood wheezing (1), and 1% of all infants are admitted to hospital due to wheezing (2). Earlier studies have shown that these children are at an increased risk of asthma in later childhood: the risk is 15–71% among children with a history of hospitalization for wheezing in infancy (3–8), whereas it is 4–10% in non-selected populations (1, 9). Nowadays, the trend in asthma therapy is to start the anti-inflammatory medication in a very early

course of the disease, in order to prevent later chronic, and even permanent, pathological bronchial changes (10). However, the identification of wheezing infants who are at risk of asthma in later childhood is difficult. Mainly, the increased risk of asthma has been related to inherited susceptibility to asthma and atopy, and to the development of clinical allergic manifestations (1). In addition, there is evidence of the role of certain infections, in particular, respiratory syncytial virus (RSV) bronchiolitis, as a factor contributing to later asthma (3, 7, 11).

The aims of the present study were to evaluate the occurrence of asthma and atopy among

school-aged children hospitalized for wheezing in infancy, and to clarify the asthma-predictive factors present in early childhood.

Materials and methods

In 1992–93, one hundred children, aged 1–23 months, were recruited into this study (12). All the children had infection-related wheezing resulting in hospital treatment (the index episode) in the Department of Paediatrics, Kuopio University Hospital (12).

The baseline data were charted using a structured questionnaire at enrolment, including age on admission, the history of earlier episodes of wheezing, the presence of atopic dermatitis, family history of asthma and atopy, maternal smoking during pregnancy, passive smoking during infancy, and pet contacts at home or at day care during infancy. In addition, total serum immunoglobulin E (IgE), blood eosinophil count, and serum eosinophil cationic protein (ECP) were determined. The total serum IgE concentration of ≥ 60 kU/l (13), the blood eosinophil count of ≥ 0.45 cells $\times 10^9$ /l (14), and the serum ECP concentration of ≥ 16 μ g/l (15) were considered as pathological. Seven common respiratory viruses, i.e. RSV, adenoviruses, influenza A and B viruses, and parainfluenza type 1, 2 and 3 viruses, were studied by antibody and antigen assays; there were 25 RSV and 18 other viral identifications (16).

During the follow-up time from the index episode of wheezing to the latest visit in 1999, five study visits were organized in order to follow-up the respiratory status and allergic manifestations in the children (17). Eighty-two children, 61 boys and 21 girls, attended the follow-up in 1999, and they constitute the subjects of the present paper. The age of the children varied from 5.6 to 8.8 years (median 7.2 years), and the time from the index episode of wheezing ranged from 5.3 to 7.2 years (median 6.3 years).

Skin prick tests (SPT) were performed for the first time at the 8-month follow-up visit, at the median age of 1.5 years (17). The allergens (ALK SPT extracts, ALK Laboratories, Copenhagen, Denmark) tested were the food allergens cow's milk, egg white, fish, and wheat, the outdoor inhalant allergens birch, timothy grass and mugwort pollens, and the indoor inhalant allergens cat and dog epithelial danders and home dust mites *Dermatophagoides pteronyssinus* and *D. farinae*.

At the follow-up visit in 1999, the allergens tested were the outdoor allergens birch, common alder, timothy grass, meadow grass and mugwort

pollens, and spores of *Cladosporium herbarum*, and the indoor allergens cat and dog epithelial danders and home dust mites *D. pteronyssinus* and *D. farinae*.

The concentrations of non-standardized allergen extracts cow's milk, fish, wheat and *C. herbarum* spores were 1:20 weight/volume, and egg white 1:100 weight/volume. Other allergen extracts were standardized, the concentrations being 10 histamine equivalent points. Histamine hydrochloride (10 mg/ml) was used as a positive control and 50% glycerol as a negative control. Wheals with a mean diameter of at least 3 mm were regarded as positive (18), and no reactions were allowed in negative controls.

The ongoing medication was registered at the follow-up visits, including the exact data on cromone and steroid maintenance medication for asthma. The need for and the type of medication was assessed by a pediatric allergist on a clinical basis independently of the authors; the principles of the step-wise asthma-treatment policy of our hospital have been published recently (19). In brief, the children with mild to moderate asthma are treated with cromones, and the children with severe asthma, and those not responding to cromone therapy, with inhaled steroids. Severity of the disease is checked twice a year by a pediatric allergist, and changes in the medication are made, if needed, accordingly.

In the follow-up study from January to March 1999, a structured questionnaire was used to record the symptoms suggestive of asthma associated with exercise, infections or allergens. In addition, physician-diagnosed (ever in life) allergic rhinitis, allergic conjunctivitis and atopic dermatitis were recorded. Allergic diseases were classified as current if there had been clinical manifestations during the preceding 12 months. The exercise challenge test was performed in all 82 children. The baseline pulmonary function was examined by flow-volume spirometry (FVS) (Medikro, Kuopio, Finland), and forced expiratory volume in 1 second (FEV₁) was the parameter used in challenge tests. 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 FEV₁ variation was less than 5%, and the printed graphic curves were appropriate and equal in shape. The highest FEV₁ value was used in later comparisons. The baseline pulmonary testing was followed by exercise that constituted of free running outdoors for 8 minutes at a heart rate of 80% or more of the predicted maximum. The heart rate was monitored by telemetry (Polar Sport Tester, Polar Elektro Ltd, Kempele, Finland) at

1-min intervals. FVS was measured 10 min after the exercise. FEV_1 changes were calculated as follows: $[(\text{pre-exercise } FEV_1 - \text{postexercise } FEV_1)/\text{pre-exercise } FEV_1] \times 100\%$.

The children's lungs were auscultated before the baseline lung function testing and immediately after the exercise. Symptoms, and auscultatory findings, if present, were recorded.

The exercise challenge test was regarded as positive if there was auscultatory wheezing present after the exercise and/or a 15% or greater fall in FEV_1 (20).

At the follow-up visit in 1999, asthma was considered to be present if (1) the patient was on a continuous maintenance medication for asthma, or if (2) she/he had suffered from repeated (≥ 2) episodes of wheezing and/or prolonged cough (≥ 4 weeks) apart from infection during the preceding 12 months reported by parents, and the exercise challenge test was regarded as positive (9).

The data were analyzed using SPSS/PC+ 9.0 software (SPSS Inc. Chicago, IL, USA). Statistical significance of the differences between the groups was assessed with the chi-squared test for proportions supplemented by odds ratios (OR) with 95% confidence intervals (CI), and predictive values (PV) for positive test results. Fisher's exact test was used when the expected frequency for any cell was < 5 . The logistic regression analysis was used to calculate the adjusted ORs and related 95% CIs. Two-tailed tests were used in all analyses. P-values less than 0.05 were considered as statistically significant.

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

Eighty-two of the original study group of 100 children were re-examined in 1999. The baseline characteristics of the 18 drop outs did not differ from the participants of the study (data not shown).

Asthma was considered to be present in 33 children (40%). Thirty of them used either cromones ($n = 18$) or inhaled steroids ($n = 12$) as maintenance medication for asthma. Despite the ongoing medication, 25 (83%) children had suffered from repeated episodes of wheezing ($n = 5$), prolonged cough ($n = 4$) or both ($n = 16$) during the preceding 12 months, and the exercise challenge test was regarded as positive in 8 (27%) cases. Among the three children with no ongoing maintenance medication for

asthma, one had suffered from repeated episodes of wheezing, and two of prolonged cough during the preceding 12 months, and all three children had positive results in the exercise challenge test.

In 49 children asthma was considered as not to be present at early school age. Among them, 12 (24%) children had suffered either from parent-reported wheezing episodes ($n = 3$) or from prolonged cough ($n = 9$) during the preceding 12 months, but none of them had a positive exercise challenge test. Likewise, two children with positive exercise challenges reported no symptoms suggestive of asthma, and were considered as non-asthmatics.

The baseline characteristics and laboratory data of the children, in relation to the presence of asthma at early school age, are presented in Table 1. There were four factors: the presence of atopic dermatitis; blood eosinophil count of $\geq 0.45 \times 10^9/l$; total serum IgE of ≥ 60 kU/l; and a history of earlier episodes of wheezing in infancy (before the index episode), which were significantly predictive for later asthma. In addition, positive SPT reactions in early childhood were significantly associated with early school-age asthma (Table 2). In contrast, RSV identification on study entry was significantly associated with a low risk of asthma, when compared with the cases without RSV or other viral identifications during the index episode of wheezing (Table 1).

Among allergic manifestations at early school age (Table 3), there was a significant association between asthma and allergic rhinitis and/or allergic conjunctivitis. In contrast, atopic dermatitis was common both in asthmatic and in non-asthmatic children, and had no such association. In SPTs, indoor allergens gave positive reactions in 34 (41%), and outdoor allergens in 28 (34%) children. Thirty-eight (46%) children had positive reactions either to indoor or to outdoor allergens, 24 of them having and 14 not having asthma ($p < 0.001$). The corresponding figures were 17 and 7 ($p < 0.001$) for the 24 (29%) children with positive reactions to both indoor and outdoor allergens.

The baseline characteristics, laboratory data, and the skin test findings in early childhood and at early school age were analyzed separately for the subgroup of 12 non-asthmatic children with asthma-suggestive symptoms (repeated wheezing or prolonged cough during the preceding 12 months reported by parents), but with no objective evidence of asthma (negative results in the exercise challenge test). Concerning the baseline characteristics, 2 (17%) of the 12 children had

Table 1. Baseline characteristics and laboratory data at the index episode of wheezing in relation to asthma at early school age

Baseline characteristics	All children n = 82	Asthma present n = 33	PV	p*	OR*	95% CI*
Family history of asthma	19	10	53%	0.1361	2.34	0.76–7.17
Maternal history of asthma	6	3	50%	0.6134	1.58	0.27–9.32
Family history of atopy	46	21	46%	0.2088	1.83	0.71–4.68
Maternal history of atopy	27	10	37%	0.4978	0.71	0.26–1.92
Passive smoking during infancy	39	16	41%	0.5981	1.28	0.51–3.25
Maternal smoking during pregnancy	20	9	45%	0.4820	1.46	0.51–4.19
A furry pet at home or at day care during infancy	25	8	32%	0.3592	0.62	0.22–1.72
Earlier episodes of wheezing in infancy	11	8	73%	0.0468	4.29	1.02–17.99
Atopic dermatitis	23	15	65%	0.0089	4.11	1.42–11.84
IgE ≥ 60 kU/l†	17	11	65%	0.0452	3.41	1.03–11.33
Blood eosinophil count $\geq 0.45 \times 10^9/l^\ddagger$	26	18	69%	0.0008	7.02	2.26–21.79
ECP ≥ 16 $\mu\text{g/l}^\S$	15	9	60%	0.1739	2.35	0.69–8.05
RSV identification	20	3	15%	0.0398	0.23¶	0.06–0.93

P-values, ORs (odds ratios) and 95% CIs (confidence intervals) were determined by logistic regression adjusted for sex and age on entry to the study. Analyses have been done separately for each factor. PVs (predictive values) were determined as percentages of positive test results (i.e. presence of corresponding characteristics or laboratory data) in asthmatics vs. all positive cases.

*Asthmatics vs. non-asthmatics.

†The samples were obtained for 78 children; asthma was present in 30 of them.

‡The samples were obtained for 79 children; asthma was present in 31 of them.

§The samples were obtained for 81 children; asthma was present in 32 of them.

¶Compared with the children with RSV not identified during the index episode of wheezing. When compared with the children with no viral identifications, the OR remained the same, 0.23 (95 % CI 0.05–0.94). The study design did not allow any comparisons with children who had not been hospitalized for wheezing in infancy.

Table 2. Skin test reactivity 8 months after the index episode of wheezing in relation to asthma at early school age

Positive SPT reactions to†	All tested children n = 77	Asthma present n = 31	PV	p*	OR*	95% CI*
Food allergens‡	10	8	80%	0.012	7.65	1.50–39.04
Inhalant allergens	20	14	70%	0.002	5.49	1.81–16.69
Indoor allergens§	17	11	65%	0.020	3.67	1.18–11.35
Outdoor allergens¶	6	5	83%	0.036	8.65	0.96–78.15
Food or inhalant allergens	22	15	68%	0.002	5.22	1.79–15.22

P-values were determined by the chi-squared or Fisher's exact test, supplied by ORs (odds ratios) and 95% CIs (confidence intervals). PVs (predictive values) were determined as percentages of positive test results (i.e. presence of corresponding characteristics or laboratory data) in asthmatics vs. all positive cases.

*Asthmatics vs. non-asthmatics.

†SPT reactions were defined as positive if the wheal had a mean diameter of ≥ 3 mm.

‡There were seven positive SPT reactions to fish, six to egg white, five to cow's milk, and four to wheat.

§There were 12 positive SPT reactions to cat dander, 11 to dog dander, and 2 to dust mite *D. pteronyssinus*.

¶The six positive SPT reactions were to birch pollen. Timothy grass and mugwort pollens gave no positive reactions.

suffered from earlier episodes of wheezing in infancy, atopic dermatitis was present in 3 (25%), total serum IgE was elevated in 1 (8%), blood eosinophilia was present in 2 (17%), and RSV was identified in 3 (25%) children. The respective figures were 24%, 45%, 37%, 58%, 9% for the 33 children with asthma present at early school age. The only statistically significant difference that was seen between the 33 asthmatics and these 12 symptomatic non-asthmatics was in the occurrence of blood eosinophilia ($p = 0.045$). There were no significant differences between the 37 non-symptomatic and the 12 symptomatic non-asthmatic children (data not shown).

The predictive factors for asthma did not change by excluding the 12 symptomatic non-asthmatic children from analyses, or by including them in the asthma group (data not shown). The only exception was elevated total serum IgE, which lost its significance on both occasions. The effect of IgE, however, remained in the same direction. Likewise, the occurrence of skin test reactivity in early childhood or at early school age did not differ between the 12 symptomatic non-asthmatic and the 33 asthmatics or the 37 non-symptomatic non-asthmatics (data not shown).

The two non-symptomatic children with positive exercise challenge had neither earlier

Table 3. Allergic manifestations and asthma at early school age

Allergic manifestations	All children n = 82	Asthma present n = 33	PV	p*	OR*	95% CI*
Allergic rhinitis	30	22	73%	< 0.001	10.25	3.60–29.22
Allergic conjunctivitis	25	19	76%	< 0.001	9.73	3.24–29.17
Atopic dermatitis	40	20	50%	0.079	2.23	0.91–5.49
Any positive SPT reactions†	38	24	63%	< 0.001	6.67	2.49–17.86
Positive SPT reactions to indoor allergens‡	34	23	68%	< 0.001	7.95	2.92–21.61
Positive SPT reactions to outdoor allergens§	28	18	64%	0.001	4.68	1.76–12.42

P-values were determined by the chi-squared test supplied by ORs (odds ratios) and 95% CIs (confidence intervals).

PVs (predictive values) were determined as percentages of positive test results (i.e. presence of corresponding characteristics or laboratory data) in asthmatics vs. all positive cases.

*Asthmatics vs. non-asthmatics.

†SPT reactions were defined as positive if the wheal had a mean diameter of ≥ 3 mm.

‡There were 29 positive SPT reactions to cat dander, 25 to dog dander, 6 to *D. pteronyssinus* and 3 to *D. farinae*.

§There were 19 positive SPT reactions to birch pollen, 19 to common alder pollen, 16 to meadow grass pollen, 15 to timothy grass pollen, 4 to *C. herbarum* and 1 to mugwort pollen.

episodes of wheezing, atopic dermatitis, elevated total serum IgE, nor blood eosinophilia on entry to the study. At early school age, one of them had allergic rhinitis and had skin test reactions to indoor allergens.

Discussion

There were three main results in the present study. First, at early school age, asthma was common after wheezing requiring hospitalization in infancy, being present in 40% of the children. The previously published figures have varied from 15% to 71% (3–8). Second, the history of earlier episodes of wheezing, atopic dermatitis, elevated total serum IgE, and blood eosinophilia in infancy, as well as early sensitization to common food and inhalation allergens were significantly predictive for later asthma. This is consistent with earlier studies (5, 6, 8, 21, 22), stressing the role of atopy in the development of asthma. On the other hand, the PVs were less than 70% for all individual atopic factors in infancy. Third, against earlier findings (3, 7), RSV identification during the index episode of wheezing was associated with a relatively favorable outcome. These three main results are in accordance with our observations in the same cohort 3–4 years earlier, when the children were at preschool age (17). However, separating ‘transient wheezers’ from ‘permanent wheezers’ (i.e. asthmatics) is difficult among preschool-aged children, and therefore, we found it worthwhile to continue following the study cohort up to school age.

The prevalence of clinically diagnosed asthma is 4% in the school-aged child population in our area (9). In the present study, the risk of asthma was 10-fold after wheezing requiring hospitalization in infancy. The risk was increased by

recurrent episodes of wheezing in infancy and the development of atopic manifestations in early childhood, being over 15-fold in both cases. As seen 3–4 years earlier in the same study cohort (17), a family history of asthma or atopy did not affect the outcome significantly, although several personal atopic markers in infancy or early childhood did. Because the maternal history of asthma is usually considered to be a stronger risk factor for asthma than is the paternal history, or the presence of asthma in siblings (23, 24), we also tested these potential asthma-predictive factors separately. The result was negative; no significant association was seen between maternal or paternal asthma or atopy, nor asthma or atopy in siblings, and later asthma at early school age. The negative result is probably due to insufficient power (20–24%) of the study to show the possible predictive effect of the family history of atopy or asthma.

Early sensitization to indoor allergens, mainly to cat and dog epithelial danders, was significantly predictive for later childhood asthma, as also seen earlier in the same study cohort (17). However, furry pet contacts in infancy did not lead to sensitization and to the development of asthma very often; the risk for asthma seemed to be even lower than in non-exposed children. Although the finding was not statistically significant, it supports the current concept (25), and our previous findings in non-sensitized children (17), that pet contacts in infancy are not necessarily harmful even for children at risk. If immunologic tolerance develops instead of atopic sensitization, such contacts may even be asthma preventing, as was seen in children with dog exposure in early life in a recent study (26). On the other hand, atopic families are often advised not to keep furry pets at home, which may have

biased the results, leading to underestimation of the role of pet contacts (17, 25).

Smoking was as common in families of later asthmatic children as in families of later non-asthmatic children. In disagreement with most other studies (1, 8, 27), passive smoking or maternal smoking during pregnancy did not significantly predict later childhood asthma. Our non-significant findings of smoke exposure are probably due to the highly selected, relatively small cohort, not allowing non-atopy-related risk factors, such as smoke exposure, to play a significant role in predicting asthma. In addition, though parental smoking was common, nearly 50%, in the present study, smoking indoors is rare in our country, particularly in families with young children (28). This, of course, lessens exposure to tobacco smoke, and may, at least partly, explain our negative results.

Earlier studies have particularly stressed the role of RSV as a factor inducing asthma (3, 7). In disagreement, RSV infection was associated with a relatively low risk for asthma, as seen also 3–4 years earlier in this cohort (17). However, if compared with a non-selected school-age population in our area, the risk was still about threefold (9). The result supports the previously presented hypothesis that the children wheezing without RSV have an intrinsic tendency to wheeze induction, e.g. by non-invasive viruses such as rhinoviruses (29). Consequently, in atopic children, early childhood wheezing may actually be the first sign of asthma (30).

The definition of asthma is crucial for the results of the present study. The definition of pediatric asthma and its severity, in particular, varies between different countries and even between different centers in the same country, leading to varying diagnostic criteria in different studies (31). In the present study, rather strict criteria were used; the patients either had to be on continuous maintenance medication for asthma, or they had to have both recurrent subjective symptoms suggestive of asthma and an objective, experimental evidence of asthma. However, the exercise challenge test employed was positive only in one-third of asthmatics. In addition, the inclusion of children on maintenance therapy carries the bias that children cured of their asthma have been registered as asthma cases. As a diagnostic approach for asthma, the exercise challenge test is known to be a very specific but rather non-sensitive test (20). It is likely most children with asthma in our study were well treated such that the ongoing anti-inflammatory medication had reduced bronchial inflammation and therefore bronchial hyperresponsiveness.

Nevertheless, more than 80% of children on maintenance were still symptomatic, having suffered from repeated wheezing or prolonged cough during the preceding 12 months, implying active asthma. In addition, the asthma-treatment policy of our hospital is to check the need of maintenance medication twice a year in young children. Thus, there is a high probability that all asthma cases in the present study were 'true', though possibly mild, asthmatics.

Among the non-asthmatic children, 12 children had been symptomatic during the preceding year. However, neither including these 12 children in the asthma group for analyses, nor excluding them from analyses, changed the main results of the present study. In addition, if a lower limit, a 10% decrease in FEV₁, was applied instead of a 15% decrease, for a positive exercise challenge test result (20), no more than 1 of these 12 children would have been regarded as asthmatic. Thus, the results of the alternative analyses did not support abandoning the used criteria for the presence of asthma, which have been approved earlier in population-based studies in our area (9, 28).

There are three major strengths in the present study. First, the study was prospective with four control visits before the present study visit. Second, the follow-up time was long, continuing from infancy up to the median age of 7.2 years. We consider the follow-up long enough, as asthma after bronchiolitis or early childhood wheezing usually begins before school age, having later, in fact, a tendency to improve in relation to age (32). Accordingly, 90% of the asthma cases in the present study had been diagnosed before the follow-up visit at school age, and third, the coverage of the study was good. Despite the long follow-up, the proportion of drop outs was only 18%, and their basic characteristics did not differ from those of participating children.

The main shortcoming of the study is the absence of a control group of children not hospitalized for wheezing in infancy. However, there are two recent studies on the prevalence of asthma at school age in the non-selected populations of our area (9, 28). In these two studies, the prevalence of asthma has been rather constant, 4% to 4.5% in the age group of 7–12 years. As the criteria for asthma in these studies were, with minor modifications, similar to the criteria applied in the present study, the figures of prevalence are comparable.

In summary, if hospitalization for wheezing occurs in infancy, more than every third child will suffer from asthma at early school age.

Recurrent wheezing in infancy, as well as the development of atopic manifestations, increases the risk significantly. In contrast, RSV seems to play a minor role in the development of asthma.

Acknowledgments

We would like to thank Ida Montin's Foundation, Kerttu and Kalle Viik's Fund, and Kuopio University Hospital (EVO grant, code 440054) for the financial support of this study. We would also like to thank Pirjo Halonen, PhD, for her kind advice in statistical analyses, and Ritva-Liisa Väättäin, RN, for practical assistance in the study.

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