Preschool asthma after bronchiolitis in infancy

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ABSTRACT

Asthma risk is lower after wheezing associated with RSV than with non-RSV infection in infancy. RSV is the main wheezing-associated virus in infants aged <6 months. We evaluated the outcome of children hospitalized for bronchiolitis at <6 months of age, with special focus on viral etiology and early risk factors.

Out of 205 infants hospitalized for bronchiolitis at <6 months of age, 127 (62%) attended the control visit at age (mean) 6.5 years, and the parents of additional 39 children were interviewed by phone. Thus, follow-up data collected by identical structured questionnaires were available from 166 (81%) children. Viral etiology of bronchiolitis, studied on admission by antigen detection or polymerase chain reaction, was demonstrable in 97% of cases.

Current asthma was present in 21 (12.7%) children. The figure was 8.2% in the 110 former RSV patients vs. 24% in non-RSV patients (p=0.01). The number of children with asthma ever in life was 45 (27%). In adjusted analyses, atopic dermatitis, non-RSV bronchiolitis and maternal asthma were independently significant early-life risk factors for asthma.

The risk of asthma is lower after RSV bronchiolitis than after bronchiolitis caused by other viruses in children hospitalized at <6 months of age.

Key words
Asthma, Atopy, Bronchiolitis, Respiratory Syncytial Virus, Rinovirus
INTRODUCTION

Bronchiolitis is the most common lower respiratory infection (LRI) in infancy (1). American Academy of Pediatrics has defined bronchiolitis as a disorder in <24 months children caused by viral LRI and characterized by acute inflammation, mucus production and bronchospasm of small airways (2). In most European countries, the upper age limit used at least in clinical practice has been 12 months (3). The severity of bronchiolitis and need for hospital care decrease by increasing age (4). The viral etiology of bronchiolitis is age-dependent; respiratory syncytial virus (RSV) is the predominant virus at <6 months and rhinovirus at >12 months of age (5). Bronchiolitis in infancy increases the asthma risk in later life (6-8). The studies with outcome data available beyond age 5 years have been made in children aged <36 months (5,9,10), aged <24 months (11,12) or aged <12 months (13,14) on admission, however, with no age-specific data available for children hospitalized at <6 months of age.

We have prospectively followed-up a group of children hospitalized for bronchiolitis at <6 months of age in 2001-2002 and in 2002-2004 (15,16). RSV was the causative agent in 70%, rhinovirus in 7% and other viruses in 7% of the cases (15). When the children were 5-6 years old, they were invited to a clinical follow-up study in 2008-2009. The hypothesis of the study was that asthma is more common after non-RSV bronchiolitis (especially after rhinovirus bronchiolitis) than after RSV bronchiolitis and more common after bronchiolitis at <3 months than at 3-6 months of age.

The aim of the present study was to evaluate the outcome with special focus on asthma at preschool age after hospitalization for RSV, non-RSV and rhinovirus bronchiolitis at <6 months of age. In addition, the age on admission for bronchiolitis and other early risk factors like asthma and atopy in parents and atopic dermatitis in children, were analyzed as predictors of childhood asthma.
MATERIAL AND METHODS

Two hundred and five healthy full-term infants aged <6 months and hospitalized for bronchiolitis in the Department of Pediatrics, Tampere University Hospital (Finland) were enrolled in the study between December 1st, 2001 and May 31st, 2002 and between October 28th, 2002 and May 31st, 2004. The Ethics Committee of the Tampere University Hospital District approved the study. An informed consent was obtained from parents before enrolling the children.

Bronchiolitis was characterized by lower respiratory infection (LRI) with rhinitis, cough and diffuse wheezes or crackles (15). The etiology of bronchiolitis was assessed in nasopharyngeal aspirates by immunofluorescence for 7 viruses including respiratory syncytial virus (RSV), and by polymerase chain reaction (PCR) for 9 viruses including RSV and rhinoviruses, and by PCR for *Bordetella pertussis* (17).

From 2008 to 2009, 127 (62%) children attended the study visit at 5-7 years of age. In addition, parents of the 39 children who did not attend the study visit were contacted and interviewed by phone. Thus, follow-up data collected by identical structured questionnaires were available from 166 (81%) children (Figure 1). Doctor-diagnosed asthma, the age when asthma had been diagnosed and the continuous or intermittent use of inhaled corticosteroids (ICS) as maintenance medication for asthma collected by year were registered. The intermittent ICS medication means a pre-set regular use during infections or respiratory symptoms. In addition, data were recorded on parent-reported wheezing episodes and episodes of other asthma-like symptoms like prolonged (>4 weeks) cough and night cough apart from infection. The presence of doctor-diagnosed atopic dermatitis and allergic rhinitis was registered; only cases symptomatic during the preceding 12 months were
included. In addition, parental doctor-diagnosed asthma and atopy (allergic rhinitis or atopic dermatitis), keeping of indoor furry pets and parental smoking during and after pregnancy were inquired. All data were collected separately for mothers and fathers.

Skin prick tests (SPT) were made in 124 children for 8 allergens: birch, timothy grass and mugwort pollens, cat and dog dander, house dust mites (*Dermatophagoides pteronyssimus* and *D. farinae*) and spores of the mold *Alternaria alternata*. Wheals with a mean diameter of 3 mm or more were regarded as positive, and no reactions were accepted to negative control. Children were not allowed to take any antihistamine medication for 5 days prior testing.

Bronchial hyper-responsiveness (BHR) was studied by exercise challenge test (ECT), which consisted of free running outdoors for 8 minutes and measurements of pre- and post-exercise airway resistance by impulse oscillometry (IOS) (Jaeger, Master Screen IOS, Höchberg, Germany). Exercise was considered sufficient when heart rate, monitored by heart rate monitor (Polar Ltd, Kempele Finland), was at least 90 % of predicted maximum for 2 minutes or longer. IOS was repeated until 3 acceptable pre-exercise and 2 acceptable post-exercise curves were obtained. The resistance curves had to be graphically appropriate and free from artifacts for the whole 30 sec measurement time. Resistance values were measured at 5 Hz level (Rrs5) and expressed as standard deviations (SD) from national height-related, gender-specific references (18). BHR was considered to be present if the best post-exercise Rrs5 value had increased 35 % or more from the best pre-exercise value (19). If the child had suffered from infection during 2 preceding weeks, IOS was rescheduled.
Current asthma was considered to be present if the child was on continuous maintenance medication for asthma, or if the child had suffered from doctor-diagnosed wheezing or from prolonged (>4 weeks) cough or night cough apart from infection during the preceding 12 months and BHR was documented in ECT. Previous asthma before the control visit was defined by the use of ICSs as continuous or intermittent maintenance medication for asthma. If the child had either previous or current asthma, the term asthma ever in life was used.

Statistics

The data were analyzed using IBM SPSS 18.0. The statistical significances of differences between the groups were calculated with t-test, Chi-square test and Fisher’s exact test. Logistic regression was used to analyze the associations between risk factors and asthma, first by univariate analyses and then by multivariate analyses adjusted for age on admission (<3 vs. >3 months), gender and characteristics which were significant in univariate analyses. Odds ratios with 95% confidence intervals (95% CI) are reported from both univariate (OR) and multivariate adjusted (aOR) analyses.

RESULTS

The mean age of the 166 children attending the study was 6.5 years (SD 0.57), and 86 (52%) were boys. Current asthma was present in 21 (12.7%) children: in 14 boys (16.3% of boys; p=0.05 vs.
girls) and in 7 girls (8.8% of girls). In addition, there were 24 children with no current asthma who had been previously, but not during the preceding 12 months, on ICSs as maintenance medication for asthma. Thus, the number of children with asthma ever in life before or during the study was 45 (27%). The age-specific prevalence and cumulative incidence of asthma, defined by the use of continuous or intermittent ICSs, are presented in Figure 2. The highest prevalence, 26.9 %, was seen at 2-3 years of age.

Eighteen children with current asthma had used ICSs during the preceding 12 months. Twelve children were on continuous and 6 on intermittent ICSs, and two of them used also leukotriene antagonists. Five (24%) children were symptomatic and six (29%) hyper-responsive in ECT despite of maintenance medication. Three additional children had symptoms consistent with asthma and were hyper-responsive in ECT, and they were defined to have asthma. BHR was documented in 5 other children, but none of them reported doctor-diagnosed wheezing or prolonged or night cough. Six (4%) of the non-asthmatic children had suffered from repeated parent-reported wheezing, but none of them reported doctor-diagnosed wheezing, prolonged or night cough nor had BHR in ECT.

RSV had caused 117(70.5%) and rhinovirus 21(12.7%) of the 166 bronchiolitis cases (Table 1). B. pertussis was involved in 10(6%) cases, but all were mixed infections with viruses. Current asthma at 6.5 years of age was present in 9(7.7%) of former RSV bronchiolitis patients (vs. 24.4 % of former non-RSV patients, p=0.01), in 3(14.3%) former rhinovirus bronchiolitis patients and in 1(10%) of former B. pertussis positive patients.
Age on admission as a continuous variable (but not categorized into <3 and > 3 months), atopic dermatitis at <12 months of age (71.4% vs. 23.4%, p<0.001) and asthma in mothers (38.1% vs. 11.0%, p=0.001) but not in fathers, were significantly associated with current asthma (Table 1). Instead, maternal smoking, paternal smoking and keeping furred pets at home during infancy had no association with later asthma (Table 1).

Forty-eight (29%) study children had suffered from symptoms presumptive for allergic rhinitis during the preceding 12 months, and 13 (27%) of them had current asthma (vs. 6.8% in those 118 with no allergic rhinitis, p<0.001). Correspondingly, 61.9% of the 21 children with and 24.1% of those 145 without asthma had allergic rhinitis. SPTs were done to 124 children; 8/15 (53.3%) children with asthma were SPT positive (vs. 6.4% of those 109 with no asthma, p=0.07). Birch pollen (22.8%), timothy grass pollen (19.2%), dog dander (12.7%) and cat dander (11.7%) were common and mugwort pollen (1.0%), home dust mites (1.0%) and spores of molds (0%) were rare allergens.

Maternal history of asthma was a significant risk factor for asthma in their children (Table 1). However, 21(87.5%) of the 24 mothers with asthma (p=0<0.001 vs. 52 mothers with no asthma) and 6(60%) of the 10 fathers with asthma (p=0.06 vs. 34 fathers with no asthma) had also doctor-diagnosed allergic rhinitis or atopic dermatitis. The association between parental asthma and atopy was so strong that their independent associations with asthma in children could not be studied, and we included only maternal asthma in the multivariate analyses.

As seen in Table 2, non-RSV bronchiolitis was an independent risk factor for preschool asthma in multivariate analyses adjusted for age on admission, gender, atopic dermatitis in infancy and
maternal asthma (aOR 3.74 95% CI 1.28-10.99). Atopic dermatitis in infancy and maternal asthma were other significant risk factors for current asthma in adjusted analyses (Table 2).

The analyses were repeated in the subgroup of 124 children with SPT results available by including SPT positivity in the model. SPT positivity was associated with an increased asthma risk in univariate analyses (OR 3.60, 95% CI 1.19-10.9) but not in multivariate analyses (aOR 2.81, 0.72-10.9). In these analyses, atopic dermatitis in infancy, non-RSV bronchiolitis and maternal asthma lost the statistical significance as risk factors of current asthma (Data not shown).

There were no significant differences in baseline characteristics like gender, age on admission and viral etiology of bronchiolitis between the 166 attendees and the 39 dropouts (Data not shown). Likewise, there were no significant differences in baseline or questionnaire-based characteristics, such as atopy, asthma and smoking in parents or atopic dermatitis in infancy and allergic rhinitis at preschool age in study children, between those 39 interviewed by phone and those 127 attending the study visit (Data not shown).
DISCUSSION

There are four main results in the present prospective follow-up study at preschool age after hospitalization for bronchiolitis at <6 months of age. First, asthma prevalence was only 12.7% at the mean age of 6.5 years. The figure is lower than the previously reported prevalence figures up to 48% after bronchiolitis in infancy (11-14,20). Second, atopic dermatitis in infancy was a significant risk factor for asthma, in line with earlier post-bronchiolitis studies (12,21,22). Third, asthma in mothers, but not in fathers, was a significant risk factor of asthma. Asthma in mothers has associated more than asthma in other family members with asthma risk in children in birth cohorts (10). And fourth, according to the study hypothesis, asthma at preschool age was more common after non-RSV bronchiolitis (24%) than after RSV bronchiolitis (8%) in infancy. This observation is in line with previous studies after early-life wheezing from Finland and Wisconsin, USA (9,20,23), but we were not able to confirm the specific role of rhinovirus etiology of bronchiolitis as an asthma predictive factor.

The prevalence of preschool asthma has varied from 15% to 48% in previous post-bronchiolitis studies (11-14,20), which means a 4- to 10-fold increase in asthma prevalence compared with non-selected populations (24). In earlier post-bronchiolitis studies from Finland and Sweden, the prevalence of asthma was 30% when the infants were hospitalized at <12 months of age (13) and 25-47% when hospitalized at <24 months of age (11,12,20). In birth cohort studies, the prevalence figures have been higher (30-60%) after wheezing in early life reflecting the inclusion of mild, parent-reported wheezing cases treated at home (9,10). In the present study after hospitalization for bronchiolitis at <6 months of age, asthma prevalence at preschool age was low, 12.7%, and even
lower, only 8.9%, after hospitalization at <3 months of age. In a recent study from Missouri, USA, the cumulative prevalence of parent-reported doctor-diagnosed asthma by age 6 years was as high as 48% after RSV bronchiolitis at age <12 months (14). The cumulative prevalence in the present study, called asthma ever in life, was not higher than 27% when only cases treated with ICSs were included.

Atopic dermatitis in infancy, parental atopy, parental asthma, especially asthma in mothers, and passive smoking, especially smoking mothers, have been linked with an increased risk for later asthma (13,20,21,25). In this study, one-third of children with atopic dermatitis presenting during the first year of life had asthma at the preschool age. The figure is higher than in earlier post-bronchiolitis studies after hospitalization at <24 months of age, which evidently have included children with less severe atopy not presenting in early infancy (12,20,22) Thus, atopy in infancy is an important risk factor for asthma in later life, and invasive RSV infections in infancy may increase, in addition to the risk of asthma, also the risk of allergy at early school age (13,14).

A recent post-bronchiolitis study from Sweden stressed the differences in the harmful effects of maternal and paternal smoking (25). Maternal smoking led to bronchial hyper-responsiveness and reduced lung function, whereas paternal smoking increased the risk of an own active smoking at teen age. Many studies, like the present study, have not been able to confirm the increased asthma risk after in utero or early-life tobacco smoke exposure (13,21,23,26). A selection bias might have occurred since passive smoking in infancy is a risk factor of bronchiolitis (27). In the present study, about 30% of mothers and 40% of fathers smoked, which is more than reported in young Finnish women (20%) and men (30%) (28).
RSV has been the predominant virus in bronchiolitis in infants aged <6 months and rhinovirus in infants aged >12 months (5). Asthma risk at preschool age after rhinovirus bronchiolitis has been 2- to 4-fold compared with RSV bronchiolitis (9,29). In line, only 8.2% of the former RSV bronchiolitis patients in our study had asthma at preschool age; actually, the figure is close to 4-6% asthma prevalence in non-selected age-specific population in our country (24). Accordingly, non-RSV bronchiolitis was a significant risk factor for preschool asthma, even after adjustment with potential confounding factors. However, no single virus was predominant in the former non-RSV group with current asthma. The mechanisms beyond the link from bronchiolitis in infancy to asthma in childhood are not known. Non-RSV bronchiolitis more likely reveals susceptible infants than directly causes later asthma (9,21,29). The role of rhinoviruses as an asthma predicting factor may be age-dependent (not to be seen in <6 months old bronchiolitis patients).

The study of Sigurs et al. (13) is the only post-bronchiolitis follow-up comparable with the present study. In that study, 47 former RSV bronchiolitis patients hospitalized at <12 months of age attended the control visit at the median age of 7.5 years, and 23% of them had asthma, compared with 3% in controls (13). In the present study, asthma prevalence at the median age of 6.5 years was substantially lower, only 8.2%, among 117 children hospitalized for RSV bronchiolitis at <6 months of age. In addition, Sigurs et al. reported that 20% of the former RSV bronchiolitis patients were sensitized to inhaled allergens documented by SPTs compared with 6% in controls (13). In our study, former RSV and non-RSV patients had the same SPT positivity rate, 29%. In the Swedish study, parental asthma was present in 45% of the infants with bronchiolitis, compared with 20% in our patients, which may partly explain the differences in the outcome at preschool age.
The main strengths of the present post-bronchiolitis study are the prospective design and the large number and the homogeneity of the enrolled patients; all were <6 months old, all needed hospital care, and as many as 166 children were followed-up over 5 years. When bronchiolitis is defined as viral LRI with wheezing at <24 months of age, which has been the practice in most earlier studies, the study population is more heterogenous consisting of patients with bronchiolitis, reactive airway disease and early-onset asthma.

The main shortcoming of the study is that population-based controls were not collected. On the other hand, the age-specific prevalence of asthma in Finnish children is well-known, being 4-6% at preschool age (24). In addition, many subgroups were rather small and thus, the study was underpowered to find many obvious associations. Data on atopic dermatitis and on family history of asthma and atopy were carefully collected, but no tests were available for allergen-specific IgE, eosinophils or eosinophilic markers which are well-known risk factors of childhood asthma after bronchiolitis (30,21). On the other hand, later asthma was so rare, and atopic dermatitis in infancy was so a strong predictive factor, that any additional data on risk factors would not have changed the main conclusions of the study.

In conclusion, asthma prevalence was low, only 12.7%, at the mean age of 6.5 years after hospitalization for bronchiolitis at <6 months of age. In agreement with the study hypothesis, non-RSV etiology of bronchiolitis was an independently significant risk factor of asthma in adjusted analyses, but in disagreement with the study hypothesis, age >3 months compared with age <3 months was not.
Table 1. Baseline data in 166 children hospitalized for bronchiolitis at less than 6 months of age, presented in relation asthma at preschool age.

<table>
<thead>
<tr>
<th>Current asthma (n=21)</th>
<th>No asthma (n=145)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at admission, in days Md (IQR)</td>
<td>113 (63-147)</td>
<td>77 (38-118)</td>
</tr>
<tr>
<td>Age at admission, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>9 (42.9)</td>
<td>93 (64.1)</td>
</tr>
<tr>
<td>&gt;3 months</td>
<td>12 (57.1)</td>
<td>52 (35.9)</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>14 (66.7)</td>
<td>72 (49.7)</td>
</tr>
<tr>
<td>RSV bronchiolitis, n (%)</td>
<td>9 (42.9)</td>
<td>108 (74.5)</td>
</tr>
<tr>
<td>Non-RSV bronchiolitis&lt;, n (%)</td>
<td>12 (57.1)</td>
<td>37 (25.5)</td>
</tr>
<tr>
<td>Atopic dermatitis &lt;12 months of age, n (%)</td>
<td>15 (71.4)</td>
<td>34 (23.4)</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy, n (%)</td>
<td>1 (4.8)</td>
<td>28 (19.3)</td>
</tr>
<tr>
<td>Maternal history of asthma, n (%)</td>
<td>8 (38.1)</td>
<td>16 (11.0)</td>
</tr>
<tr>
<td>Paternal history of asthma, n (%)</td>
<td>0 (0.0)</td>
<td>10 (6.8)</td>
</tr>
<tr>
<td>Maternal history of atopy, n (%)</td>
<td>13 (61.9)</td>
<td>60 (41.4)</td>
</tr>
<tr>
<td>Paternal history of atopy, n (%)</td>
<td>8 (38.1)</td>
<td>32 (22.1)</td>
</tr>
<tr>
<td>Maternal smoking in infancy, n (%)</td>
<td>5 (23.8)</td>
<td>42 (29.0)</td>
</tr>
<tr>
<td>Paternal smoking in infancy, n (%)</td>
<td>9 (42.9)</td>
<td>61 (42.1)</td>
</tr>
<tr>
<td>Furry pet at home in infancy, n (%)</td>
<td>5 (23.8)</td>
<td>46 (31.7)</td>
</tr>
</tbody>
</table>

Student’s t-test was used for continuous variables and Pearson’s chi-square test or Fisher’s exact test # for categorized variables.

< Rhinovirus in 3 cases, Influenza A virus in 3 cases, parainfluenza type 3 virus in 3 cases, adenovirus in 1 case and human metapneumovirus in 1 case, and 2 cases with no viral etiology.
Table 2. Logistic regression: Risk factors for asthma at the mean age of 6.5 years. n=166

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Crude n</th>
<th>OR (95% CI)</th>
<th>Multivariate n</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 3 months at admission</td>
<td>64</td>
<td>2.31 (0.91-5.85)</td>
<td>2.04</td>
<td>(0.69-6.04)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>86</td>
<td>2.03 (0.77-5.32)</td>
<td>2.01</td>
<td>(0.64-6.29)</td>
</tr>
<tr>
<td>Atopic dermatitis at &lt;12 months of age</td>
<td>49</td>
<td>8.16 (2.94-22.7)</td>
<td>7.45</td>
<td>(2.45-22.89)</td>
</tr>
<tr>
<td>Non-RSV bronchiolitis</td>
<td>50</td>
<td>4.04 (1.57-10.36)</td>
<td>3.74</td>
<td>(1.28-10.99)</td>
</tr>
<tr>
<td>Maternal history of asthma</td>
<td>24</td>
<td>4.96 (1.78-13.79)</td>
<td>3.39</td>
<td>(1.03-11.24)</td>
</tr>
</tbody>
</table>

Multivariate analyses were performed as adjusted for age on admission, gender, atopic dermatitis in infancy, viral etiology of bronchiolitis and maternal asthma.

Figure 1. Flow chart of study population
Figure 2. The age-specific prevalence and cumulative incidence of asthma, defined by the use of inhaled corticosteroids, in the 166 study subjects


