Common Respiratory Infections Early in Life May Reduce the Risk of Atopic Dermatitis

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Infections that occur early in life may protect against atopic disease later in life. To investigate the relationship between common acute respiratory infections and atopic dermatitis in early childhood, we closely observed a cohort of 329 children from the ages of 2 to 24 months. We assessed the effect of proven viral infections and acute otitis media on the occurrence of atopic dermatitis. If the child had his or her first respiratory infection before the age of 6 months, the child’s remaining risk of developing atopic dermatitis was reduced by 49% (95% confidence interval, 24% to 79%). The individual risk of developing atopic dermatitis was similarly reduced after infection experienced at ≥6 months of age, but the remaining risk was low, because most cases of atopic dermatitis had manifested by this time. Our results are consistent with the hypothesis that early infections may reduce the risk of atopic disease.

During the 1980s and 1990s, both the prevalence and severity of atopic diseases increased in developed countries [1–3]. Notwithstanding the strong genetic element in atopy, the increase has been explained by the following environmental factors: changes in diet and early exposure to allergens, altered living conditions, and, more recently, a decrease in the extent of exposure to many infectious diseases as a result of better hygiene conditions and immunization programs [4]. In 1989, Strachan [5] presented a theory, known as the “hygiene hypothesis” or “infection hypothesis,” according to which common infections that occur early in infancy may provide protection against atopic sensitization.

The immunologic basis for the suggested capability of infectious diseases to prevent the manifestation of atopic disease derives from the identification of 2 functionally different subsets of T-helper lymphocytes. The T-helper 2 (Th2) lymphocytes, when stimulated with allergens, release IL-4 and IL-13, which favor IgE production, whereas T-helper 1 (Th1) lymphocytes inhibit IgE synthesis by secreting IFN-γ and IL-12. The production of these latter cytokines is stimulated by viral or intracellular bacterial infections. Consequently, cytokine response to such infectious agents may switch the Th2-skewed immunity of the newborn toward a balance of the Th1-Th2 phenotype [6].

Provided that the hygiene hypothesis holds true, there are certain criteria that the infection or infections must fulfill to play an important—and demonstrable—role in the prevention of atopic sensitization. First, the infections must be ubiquitous in developed as well as developing countries, because the majority of infants (even those genetically predisposed to atopy) still do not experience atopic diseases. Second, the infections should occur very early in life, because the pattern of immune responsiveness to allergens is consolidated during the first months of life [7]. The epidemiologic data presented thus far are fragmentary and have emphasized such infectious diseases as measles, hepatitis A, and tuberculosis [8–11], which do not necessarily...
fulfill these criteria. There is a clear need to prove the causality and to compare the timing between infections and atopy.

Accordingly, we hypothesized that there is an inverse relationship between acute respiratory infections—which are ubiquitous in occurrence and start very early in life [12]—and atop disease in early childhood. We had a chance to address this issue in connection with the Finnish Otitis Media (FinOM) Cohort Study, in which we observed a cohort of children from the ages of 2 to 24 months [13, 14], with a focus on common respiratory infections, including acute otitis media (AOM). Atopic dermatitis, a chronic inflammatory skin disease commonly seen in patients with a family history of asthma and allergic rhinitis, is typically the first manifestation of atop disease [15]. In our analysis, we paid special attention to the temporal interrelation between these conditions.

**Patients and Methods**

**Study cohort and clinical follow-up.** The study population consisted of an unselected cohort of 329 healthy infants in the city of Tampere, Finland, who were enrolled in the FinOM Cohort Study, a prospective study that assessed the natural course of pneumococcal infections (carrier and otitis media), as well as risk factors for otitis media [13, 14]. The children were observed at a special study clinic from 2 to 24 months of age. During the follow-up period, each child made 10 scheduled visits to the study clinic, at the ages of 2, 3, 4, 5, 6, 9, 12, 15, 18, and 24 months. At each visit, 1 of the 2 study physicians (usually R.S.) examined the child and recorded the findings on a structured case report form. Examination of the skin (of the undressed child) was an integral part of each visit and was performed and documented as instructed in the study-specific standard operating procedure.

In addition to these visits, the study physician examined the child at the study clinic whenever the child had symptoms and signs of respiratory infection, especially if the parents suspected AOM. At these sick visits, a nasopharyngeal aspirate sample was obtained for virus detection. In cases of AOM with effusion and marked symptoms, the study physician performed a myringotomy and obtained middle ear fluid (MEF) samples for virus detection. In cases of AOM with effusion demonstrated by collection of MEF sample.

**Definitions.** The clinical diagnosis of AOM is far from straightforward. Because the inclusion of questionable cases of AOM could have biased the results, we decided to include only AOM events confirmed, as defined below, in the analyses.

“AOM” was defined as a visibly abnormal tympanic membrane (with regard to color, position, and/or mobility) suggesting middle-ear effusion, with ≥1 of the following symptoms or signs of acute infection: fever, earache, irritability, diarrhea, vomiting, acute otorrhea not caused by otitis externa, and other symptoms of respiratory infection [18]. We defined a “confirmed AOM event” as a case in which AOM was diagnosed and middle ear effusion demonstrated by collection of ≥1 MEF sample.

Viral infection was diagnosed if the patient had symptoms and/or signs of acute infection (i.e., fever, earache, irritability, diarrhea, vomiting, acute otorrhea not caused by otitis externa, or other symptoms of respiratory infection), and the presence of virus in the nasopharyngeal aspirate specimen was demonstrated by antigen detection, PCR, or culture. “Respiratory infection” was defined as a case that fulfilled the criteria for AOM (including an MEF sample collected after effusion), viral infection, or both. To avoid bias in the results, we applied strict criteria in the definitions of infections. We considered demonstration of virus in the nasopharynx or collection of an MEF sample after effusion to be evidence hard enough to support the assumption that the symptoms and signs of the patient were actually caused by an infection.

“Atopic dermatitis” was defined as described by Hanifin and Rajka [19]. For the diagnosis of atopic dermatitis, we required that the following features of eczema be detected: pruritus, facial/extensor involvement, and chronic relapsing course. The latter criterion was fulfilled if there was manifest eczema on >3 occasions, as documented at scheduled doctor visits to the study clinic or the department of Pediatrics or Dermatology at Tampere University Hospital. Two of the investigators (E.I. and T.H.), who were unaware of the infection statuses of the children in the study, reviewed the consistency of these diagnoses. We defined the “onset time of atopic dermatitis” as the date of the visit to the study clinic or university hospital at which
symptoms and signs suggestive of atopic dermatitis were first recorded in an infant later confirmed to be atopic.

**Statistical analysis.** We used survival analysis to assess the temporal and, therefore, potentially causal relationship between infections and atopic disease. Onset of atopic dermatitis was the studied outcome event, whereas the infection of interest (AOM or viral or respiratory infection) was the grouping variable. Data for children who did not complete follow-up were included in the analysis but censored at the time of dropout.

We used the Cox proportional hazards model with time-dependent covariates to assess the potential effect of infections on subsequent atopic dermatitis. The individual hazard model was formed as follows: \( \lambda(t) = \lambda_0(t) \exp[aI_i(t) + \beta A_i(t)] \), where \( \lambda_0 \) is a common baseline hazard. The indicator \( I_i(t) \) has a value of 1 after infection and 0 before that. Thus, at the onset of infection, the child moved from a state of “preinfection” to “postinfection,” and it was assumed that the change in the child’s state affects the rate of upcoming atopy multiplicatively.

Because we did not expect the effect of infection on the risk of atopy, if there was any effect, to be the same at all ages, we modeled the effect of age at the time of the first infection by adding another time-dependent indicator, \( A_i(t) \), to the model for children having infection at the age of \( \geq 6 \) months. Thus, \( A_i(t) \) has a value of 1 for infection experienced at or after the age of 6 months and 0 for infection experienced before that age. The parameter \( \alpha \) represents the effect of infection experienced at the age of \( < 6 \) months on the rate of atopy, and the sum of parameters \( \alpha \) and \( \beta \) represents the effect of infection experienced at or after age 6 months. The precision for the sum of parameters was obtained by calculating the sum of their variances and covariances. We eventually calculated the reduction in the rate of atopy by subtracting the relative risk from 1.

We chose the cutoff age of 6 months for the time-dependent indicator because review of the survival curve showed a clear change in the incidence of atopy at the 6-month point. In addition, we produced a graphical illustration of the Cox model, projected survival curves for hypothetical children having infection at age 3 or 9 months or not at all.

**RESULTS**

**Infection history of the children.** Of the 329 subjects enrolled (171 girls and 158 boys), 281 (85%) completed follow-up. Altogether, the children made 3026 scheduled visits and 2122 visits due to sickness for the evaluation of AOM or other respiratory infection. During the study period, the study children had AOM diagnosed at 871 sick visits, and \( \geq 1 \) MEF sample was obtained for 772 AOM events (89% of all events), which were thus considered to be confirmed events. Of the 772 AOM events, *Streptococcus pneumoniae* was isolated in 201 (26%), *Moraxella catarrhalis* in 177 (23%), and *Haemophilus influenzae* in 174 (23%) [13]. The total number of viral infections was 837 [14]. Not surprisingly, rhinovirus was the most common virus to be isolated: it was detected in 579 viral infections (69%). RSV was the second most common virus detected (in 123 infections [15%]). In all, there were 1286 cases of respiratory infection, 323 of which were both confirmed AOM events and viral infections.

Of the 203 children (62%) who experienced \( \geq 1 \) confirmed case of AOM during the follow-up period, only 56 (28%) had the first attack before 6 months of age. Similarly, of the 251 children (76%) who experienced viral infection, and of the 263 children (80%) who had any respiratory infection during the follow-up period, 73 (29%) and 93 (35%) had their first infection before they were 6 months of age, respectively (figure 1).

**Atopic history of the children.** Atopic dermatitis was diagnosed in 53 children (16%) in the study; in 37 (70%) of the 53 it was diagnosed before 6 months of age. None of the patients developed other atopic diseases during the study period, which
reflects the fact that atopic dermatitis frequently represents the first manifestation of atopic disease. The age distribution for the onset of atopy is shown in figure 1.

Infections and atopy. Tables 1 and 2 present the incidences of atopic dermatitis in children with no history of infection and those who were observed after an infection. As shown in table 1, the incidence of atopic dermatitis from age 2 to 5 months was 39 cases per 100 person-years among those who did not have AOM, viral, or any respiratory infection by the age of 6 months, whereas the incidence was only 10.2 cases per 100 person-years after AOM, 17.7 cases after viral infection, and 20.0 cases after respiratory infection. After the first 6 months of age, the overall incidence of atopic dermatitis was lower than the incidence before that age, but the same difference was observed between the children with no infection compared with those who had experienced AOM and/or viral infection at least once (table 2 and figure 2).

If the child had the first case of AOM before 6 months of age, she or he had, from the time of the AOM onward, a 58% lower risk of developing atopic dermatitis than she or he would have had without the infection (95% CI, −38% to 87%). The corresponding apparent reduction in the risk of atopic dermatitis was 45% (95% CI, −45% to 79%) after the first viral infection and 49% (95% CI, −24% to 79%) after the first respiratory infection, provided the infection was experienced before the patient was 6 months old. The calculated individual risk of developing atopic dermatitis was similarly reduced after infection experienced at ≥6 months of age. The first AOM at this age reduced the risk by 35% (95% CI, −97% to 79%), the first viral infection reduced the risk by 54% (95% CI, −43% to 85%), and the first respiratory infection reduced the risk by 36% (95% CI, −81% to 77%).

**DISCUSSION**

The results of the present study show a trend suggesting that common respiratory infections might protect against atopic dermatitis in childhood. The earlier in the child’s life that these infections occur, the greater their effect on the total number of children with the atopic manifestation, because of the very early occurrence of the latter. Although an infection that occurs relatively late (for example, at 9 months of age) appears to result in an almost similar percentage of decrease of the remaining risk of the atopic phenotype, its overall effect will be small, because most cases of atopic dermatitis have already been manifested by this time.

The immune environment of the fetus appears to be directed toward a Th2 response as a result of production of the cytokine IL-4 by the amnion and placenta [20]. Later manifestations of the Th2 phenotype may include enhanced IgE production, eosinophilia, and atopic disease. A deficiency of Th1-related processes, such as production of IL-12 and IFN-γ, may further

<table>
<thead>
<tr>
<th>Infection, incidence</th>
<th>No infection a</th>
<th>After infection experienced at age &lt;6 months a</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM</td>
<td></td>
<td></td>
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<tr>
<td>Cases of atopic dermatitis, no.</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up years, no.</td>
<td>91.4</td>
<td>9.8</td>
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<tr>
<td>Incidence of atopic dermatitis/100 person-years</td>
<td>39.4</td>
<td>10.2</td>
</tr>
<tr>
<td>Viral infection b</td>
<td></td>
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</tr>
<tr>
<td>Cases of atopic dermatitis, no.</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
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<td>11.3</td>
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<tr>
<td>Incidence of atopic dermatitis/100 person-years</td>
<td>38.9</td>
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<tr>
<td>Respiratory infection d</td>
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<td></td>
</tr>
<tr>
<td>Cases of atopic dermatitis, no.</td>
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<td>3</td>
</tr>
<tr>
<td>Follow-up years, no.</td>
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<td>15</td>
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<tr>
<td>Incidence of atopic dermatitis/100 person-years</td>
<td>39.4</td>
<td>20.0</td>
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</table>

a The observed differences between the “no infection” and “after infection” states failed to reach statistical significance.

b In each case of AOM, the presence of middle ear fluid effusion was demonstrated by collection of ≥1 middle ear fluid sample.

c In each viral infection, the presence of virus in a nasopharyngeal aspirate specimen was demonstrated by antigen detection, PCR, or culture.

d Respiratory infection was a case that fulfilled the criteria for AOM (including collection of a middle ear fluid sample after effusion), viral infection, or both.
increase the risk for consolidation of the Th2-skewed response pattern [21]. The longer such deficiency continues, the greater the risk. Given the capacity of many infectious agents to stimulate production of IL-12 and IFN-γ [22], the hypothesis that frequent infections that occur early in infancy induce Th1 responses, and thereby suppress Th2 responses and prevent atopic sensitization [5], seems reasonable.

Reports published elsewhere about the effect of infections on the development of allergy have been conflicting. First, there are studies that have indicated that respiratory infections (in particular Epstein-Barr virus, RSV, and rhinovirus infections [23–25]) potentially provoke the symptoms and conceivably promote the development of asthma. Furthermore, it has been suggested that allergic disease itself is a risk factor for certain infectious diseases, like otitis media—that is, individuals who have established allergic disease might be more prone to infections [26]. Finally, these notions have been supplanted by observations that children in day care centers, who are known to have an increased number of infections, do not have more cases of atopic disease than do children cared for at home [27].

In the study by Kramer et al. [28], the prevalence of atopy was lower in children who started to attend a day care nursery at a younger age than it was among those who entered a day care nursery at an older age. Several reports of epidemiologic and experimental research have supported the suggestion that infection at the time of primary sensitization may result in the suppression of IgE antibody responses [8–10, 29, 30]. Indirect evidence is provided by recent studies that have shown that cases of atopy and the number of children in the family are inversely proportional, which could be due to greater microbial exposure at an early age in families with more children [5, 31]. A problem with many of these studies is that they have studied adults or children aged >2 years—that is, individuals whose atopic phenotype has been consolidated. Here, we observed a cohort of children starting at 2 months of age and were therefore able to take into account the temporal sequence of infections and onset of atopic disease.

In our closely observed cohort, the first respiratory infection experienced at any time during the follow-up period, up to 18 months of age, approximately halved the child’s remaining risk of developing atopic dermatitis. The separate effects of myringotomy-ascertained AOM and a proven viral infection were indistinguishable from the effect of a combination of these 2 events, a respiratory infection. Our results conform with those reported recently by Illi et al. [32]. Illi and colleagues observed a cohort of 1314 children from birth and found that children who had >1 upper respiratory infections during the first year of life were at one-half the risk of developing asthma by age 7 years, as were children with no more than 1 infection.

The effect of the infection on the child’s final chance of being spared from atopic dermatitis was greater if the first infection occurred during the first 6 months of life than it was if the

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**Table 2. Incidence of atopic dermatitis among 6–24-month-old children who had not experienced acute otitis media (AOM), viral infection, or respiratory infection, and the incidence in those observed after they had experienced the respective infection for the first time at the age of <6 or ≥6 months.**

<table>
<thead>
<tr>
<th>Infection, incidence</th>
<th>No infection</th>
<th>After infection experienced before age 6 monthsa</th>
<th>After infection experienced at age ≥6 monthsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOMb</td>
<td>Cases of atopic dermatitis, no.</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Follow-up years, no.</td>
<td>189.9</td>
<td>72.7</td>
</tr>
<tr>
<td></td>
<td>Incidence of atopic dermatitis/100 person-years</td>
<td>5.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Viral infectionc</td>
<td>Cases of atopic dermatitis, no.</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Follow-up years, no.</td>
<td>141.3</td>
<td>91.0</td>
</tr>
<tr>
<td></td>
<td>Incidence of atopic dermatitis/100 person-years</td>
<td>7.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Respiratory infectiond</td>
<td>Cases of atopic dermatitis, no.</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Follow-up years, no.</td>
<td>120.4</td>
<td>117.4</td>
</tr>
<tr>
<td></td>
<td>Incidence of atopic dermatitis/100 person-years</td>
<td>7.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>

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*a The observed differences between the “no infection” and “after infection” states failed to reach statistical significance.
*b In each case of AOM, the presence of middle ear fluid effusion was demonstrated by collection of >1 middle ear fluid sample.
*c In each viral infection, the presence of virus in a nasopharyngeal aspirate specimen was demonstrated by antigen detection, PCR, or culture.
*d Respiratory infection was a case that fulfilled the criteria for AOM (including collection of a middle ear fluid sample after effusion), viral infection, or both.
Figure 2. Individual curves on the probability of not developing atopic dermatitis for 3 hypothetical children.

first infection occurred later, because the incidence of atopic dermatitis was highest during the ages of 2–5 months. These relationships are clearly illustrated in figure 2, which shows the contrasting effect of respiratory infections at 3 months of age versus 9 months of age. It is important to realize that, in most cases, atopic dermatitis started very early, during the very first months of life (70% of cases occur before the age of 6 months), whereas the incidence of respiratory infections continued to increase after the first 6 months of age and peaked shortly before the children reached the age of 12 months.

The cytokine milieu, in which the immunocytes mature, seems to play a central role in redirecting the immunology response pattern away from the atopic Th2 phenotype of the newborn, and infections favoring the Th1 type of response are important in regulating the cytokine milieu. Our findings as a whole—despite the small number of cases studied, which prevented the results from reaching statistical significance—are consistent with the hypothesis that early respiratory infection may protect against atopic disease.

Acknowledgments

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