CLINICAL REPORT

Incidence, Serum IgE and TARC/CCL17 Levels in Atopic Dermatitis Associated with Other Allergic Diseases: An Update from the Ishigaki Cohort

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Population cohort studies are important for understanding the current status of the target disease and its relation to comorbidity, gender, age, or environmental factors. To better understand atopic dermatitis (AD) and its related diseases, we initiated in 2001 a population cohort study of nursery school children from Ishigaki Island, Okinawa, Japan. The cohort study comprised a dermatologist-based physical examination, questionnaire administration, and blood sample analysis. The mean prevalence of AD was 6.3%. Questionnaire-based bronchial asthma and egg allergy in the children and paternal and sibling AD were statistically significant risk factors for AD. Boys with AD had a high incidence of asthma that was coexistent with a high serum total immunoglobulin E level. Also a high incidence of egg allergy was associated with greater AD severity as assessed by TARC/CCL17. Key words: atopic dermatitis; prevalence; incidence; cohort; epidemiology.

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Study design
The study design has been previously described (7). Briefly, the KIDS cohort comprises a dermatologist-based physical examination, questionnaire survey of the children’s parents or guardians, and analysis of collected blood samples. The study was approved by the Ethics Committee of Kyushu University and the directors and classroom teachers of the nursery schools. The parents or guardians provided written informed consent for participation of the children.

Ishigaki Island is located approximately 410 km southwest from the main island of Okinawa and has a subtropical oceanic climate. The mean annual temperature and humidity are 24.4°C and 73.1%, respectively, which are higher than those of Tokyo, Japan (16.5°C and 60%, respectively).

Physical examination and questionnaire
Dermatologists from the Department of Dermatology, Kyushu University Hospital, conducted medical skin examinations of the children since 2001. AD was diagnosed according to the Japanese Dermatological Association’s diagnostic criteria for AD (10). The parents or guardians of the children completed a structured questionnaire that included the children’s personal history of allergic diseases such as AD, allergic rhinitis (AR), bronchial asthma (BA), and food allergy. The current form of the questionnaire has been used since 2006.

Measurement of serum TARC and total IgE levels
Serum TARC levels were measured using enzyme-linked immunoabsorbent assay (ELISA, Shionogi & Co., Ltd., Osaka, Japan), according to the manufacturer’s protocols. Serum total
IgE levels were determined using radioimmunoassay (Shionogi & Co., Ltd., Osaka, Japan), as previously described in detail (8).

Statistical analysis
The Mann-Whitney U test was used to compare variables between the 2 groups. Gender-based difference in the incidence of allergic diseases and the association between AD and other allergic diseases were examined using the χ²-test or Fisher’s exact test, depending on the variable distribution. Univariate and multivariate logistic regression analyses were used to assess risk factors for AD incidence. A p-value <0.05 was considered statistically significant.

RESULTS

Study population
In total, 7,856 nursery school children aged ≤6 years from approximately 13 nursery schools participated in the KIDS cohort from 2001 to 2011. The data of AD prevalence from 2001 to 2004 were taken from our previous report (7). The data on serum total IgE levels were obtained from a total of 2,841 blood samples (1,507 boys and 1,334 girls) collected from 2001 to 2009, after excluding data of individuals duplicated in later years, if any, to avoid the possibility of children with any allergic diseases participating more often than healthy children, which would potentially affect mean total IgE values. For assessing disease risk factor, we examined questionnaires from 2006 to 2008, excluding data of individuals duplicated in later years, if any, to collect as much information on the examinee’s incidence of each disease. We used the data obtained from blood samples of 743 nursery school children in 2008 in order to assess the relation between disease severity and AD-related comorbidities.

Incidence of AD-related allergic diseases and risk factors for AD
The mean annual prevalence of AD through the 11 years in the KIDS cohort was 6.3%. The mean prevalence of AD in boys was 5.7%, and that of girls was 7.0%; the prevalence rates did not significantly differ between the 2 genders (Table SI1).

From 2006 to 2008, 1,195 answers to the questionnaires were obtained from 658 boys and 537 girls. The results of the questionnaire regarding incidental AD and related allergic diseases such as AR, BA, and food allergy (mostly egg allergy [EA]) based on gender are shown in Table I. The AD incidence (during infancy) in boys and girls was 13.2% and 14.4%, respectively, with no gender-based difference. The AR incidence in boys and girls was 3.1% and 2.5%, respectively, with no gender-based difference. The incidence of BA in boys and girls was 17.4% and 11.9%, respectively, with a statistically significant difference (p = 0.008). Among food allergies, EA was the most prevalent (67.1%) and has sufficient numbers for subsequent analysis; therefore, EA incidence was used to represent food allergy. In the questionnaire, a total of 54 children were identified as having been diagnosed as EA. Excluding 7 children identified in 2007 whose questionnaire lacked the free field regarding detailed symptoms of food allergy due to a printing problem, 30 out of the remaining 47 patients (63.8%) referred to their detailed symptoms as having eczema/urticaria (86.7%), itching only (6.6%), diarrhoea (3.3%) and a positive skin patch test (3.3%). The EA incidence in boys and girls was 5.3% and 3.8%, respectively. When nursery school children were divided into incidental AD and non-AD groups regardless of gender, the AR incidence in AD and non-AD groups was 5.5% and 2.4%, respectively. The BA incidence was 28.1% and 12.9%, and the EA incidence was 18.4% and 2.3%, respectively. All allergic diseases known as AD-related diseases examined in the questionnaire showed significantly higher disease incidence rates in the AD group than in the non-AD group (Table II). Specifically, the difference in EA incidence between the AD and non-AD groups was remarkable. Univariate analysis of familial history of allergic diseases revealed that incidences of paternal AD, AR, and BA; maternal AD and food allergy; and sibling AD and AR were significantly associated with the subjects’ AD incidences. Further, multivariate logistic regression analysis, including age, gender, and incidence of other allergic diseases of the subject’s and family history of allergy, revealed that the incidences of subject’s BA and EA and paternal and sibling AD were statistically significant risk factors for AD as determined by an odds ratio > 2 (Table SII1).

### Table I. Incidences of allergic diseases based on gender of nursery school children from Ishigaki Island

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
<th>p-values</th>
<th>χ²-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (%)</td>
<td>n</td>
<td>n (%)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>571</td>
<td>87 (13.2)</td>
<td>460</td>
<td>77 (14.3)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>632</td>
<td>20 (3.1)</td>
<td>517</td>
<td>13 (2.5)</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>536</td>
<td>113 (17.4)</td>
<td>466</td>
<td>63 (11.9)</td>
</tr>
<tr>
<td>Egg allergy</td>
<td>614</td>
<td>34 (5.3)</td>
<td>508</td>
<td>20 (3.8)</td>
</tr>
</tbody>
</table>

*% of total number of children.*

Table II. Atopic dermatitis (AD)-associated allergic diseases in nursery school children from Ishigaki Island

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>Non-AD</th>
<th>p-values</th>
<th>χ²-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (%)</td>
<td>n</td>
<td>n (%)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>154</td>
<td>9 (5.5)</td>
<td>995</td>
<td>24 (2.4)</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>115</td>
<td>45 (28.1)</td>
<td>887</td>
<td>131 (12.9)</td>
</tr>
<tr>
<td>Egg allergy</td>
<td>122</td>
<td>30 (18.4)</td>
<td>1,000</td>
<td>24 (2.3)</td>
</tr>
</tbody>
</table>

*% of total number of children. *Fisher’s exact method.
Serum total IgE levels in children from Ishigaki Island

The analysis of blood samples of children obtained from 2001 to 2009 revealed an increase in serum total IgE levels from the age of 2 years, and the levels in boys from the age of 2–4 years were significantly higher than those in girls of the same age (Fig. 1). When children were divided into groups based on whether they had allergic disease or not, according to the data from the questionnaire 2006–2008, the mean total IgE levels in incidental AD and non-AD children were 425.3 ± 678.3 IU/ml and 141.9 ± 315.4 IU/ml, respectively; the levels for those with incidental AR and non-AR were 454.8 ± 592.4 IU/ml and 172.7 ± 385.0 IU/ml, respectively; the levels for those with incidental BA and non-BA were 328.3 ± 505.6 IU/ml and 157.3 ± 376.6 IU/ml, respectively; and the levels for those with incidental EA and non-EA were 496.7 ± 784.6 IU/ml and 164.1 ± 358.0 IU/ml, respectively (graphs not shown). These mean total IgE levels in the incidental disease groups of each allergic disease were statistically higher than those in the non-incident groups (p < 0.01). In incidental AD children with coexistent BA, but without AR or EA, the serum total IgE levels increased significantly compared to incidental AD children without BA (Fig. 2).

Disease severity in children with AD and EA obtained from answers to the questionnaire

Among the 743 children examined in 2008, blood samples were successfully obtained from 696 children, from whom we received 520 valid answers to the questionnaire. The mean TARC levels of non-allergic children decreased with age, while those of the AD group did not change with age (Fig. 3).

Among the 520 valid answers on EA history, TARC and total IgE levels were measured for 520 and 519, respectively. The mean TARC and total IgE levels of the children with EA history were 733.5 ± 461.1 pg/ml and 385.7 ± 580.4 IU/ml, respectively, while those in children without EA history were 554.0 ± 371.1 pg/ml and 181.0 ± 324.0 IU/ml, respectively. The TARC and total IgE levels in children with EA history were significantly higher than those in children without EA history (graphs not shown). We obtained 31 answers for EA history in the group with AD, and serum TARC levels were measured for 30 out of the 31. The mean TARC levels of the AD children with EA history was 965.0 ± 487.8 pg/ml, while that of AD children without EA history was 703.5 ± 440.0 pg/ml. The serum TARC level in incidental AD children with EA history was significantly higher than in those without EA history (Fig. 4).

DISCUSSION

The AD incidence assessed by questionnaire (13.7% in total) was considerably higher than the AD prevalence assessed by physical examination (6.3% in annual average) because those with incidental AD included a population who had AD but had remitted naturally at the time of examination in the present study. Most infantile AD cures or remission occurred naturally. Additionally, in the follow-up of the KIDS study, we found that AD in 71.6% of the children who were diagnosed by dermatologists alleviated naturally within 3 years (7), explaining the gap between the AD incidence rate via the answers to the questionnaire and the mean annual AD prevalence.

The AD prevalence on Ishigaki Island was apparently lower than that reported by Yamamoto S where from 2000 to 2002, a research team of the Japanese Ministry of Health, Labour, and Welfare examined 48,072 children living in Asahikawa, IWate, Tokyo, Gifu, Osaka, Hiroshima, Kochi, and Fukuoka (11). They reported that the national mean prevalence of AD was 12.8% in individuals aged 4 months, 9.8% in those aged 18 months, 13.2% in those aged 3 years, 11.8% in those aged 6–7 years, 10.6% in those aged 12–13 years, and 8.2% in those aged 18 years (11). The AD prevalence on Ishigaki Island (6.3%) was approximately half that of correspondingly aged children in mainland Japan. There are many possible explanations for this, such as different pathogens, dietary habits, or flora. However, we believe that the high temperature (24.4°C) and humidity (73.1%) of Ishigaki Island might reduce the
Incidence of atopic dermatitis from the Ishigaki cohort

AD incidence, presumably reducing AD onset in those who have filaggrin mutation (12) or a defect of filaggrin-digesting enzyme (13). Indeed, a genetic analysis in the KIDS cohort in collaboration with the Department of Dermatology, Keio University School of Medicine, did not find a positive association between filaggrin mutations and AD incidence in Ishigaki Island children (14).

There was a gender difference in total IgE levels (significantly higher in boys aged 2–4 years than girls of the same age group) (see Fig. 1). Serum total IgE levels are increased in children with any allergic disease (either AD, AR, BA, or EA), as shown elsewhere; however, in our study, only BA showed a significantly higher disease incidence in boys (see Table I). In addition, BA coexistence alone further increased serum total IgE levels in children with AD. Therefore, we believe that the gender difference in total IgE levels may be because of the high BA incidence in the boys in our study. We further examined whether there is a gender difference of TARC levels since severity of AD is reported to be associated with prevalence of asthma (15) and serum IgE levels (16). However, there was no significant gender difference between boys and girls by age in the present study (Fig. S1).

Another interesting finding was a high coexistence of EA in children in the incidental AD group. The coexistence of EA in children with AD was 7.9 times higher than that in children without AD. This rate was considerably higher than the rates in other diseases (AR or BA), which were approximately 2 times (Table II). Incidental EA was also a significant risk factor for AD (Table SII'). These data indicate an intimate relation between AD and EA. Another interesting finding was that the serum TARC levels, a disease severity marker, in children with AD and EA were significantly higher than those in children without EA (see Fig. 4). The serum TARC levels reflect disease severity of infantile AD (17, 18), and AD severity appears to be correlated with the degree of EA (19). The significant increase in TARC levels in children with AD and EA in the present study may indicate that EA comorbidity might be an important exacerbation factor in children with AD, although we currently do not know whether it is really causative or a bystander. Alternatively, children with more severe AD may be prone to EA, presumably by repeated percutaneous sensitisation through the impaired barrier in the lesional skin.

In conclusion, we obtained the current status of AD and other associated allergic diseases in children from Ishigaki Island. Subjects’ BA and EA and paternal and sibling AD were statistically significant risk factors for AD. We found that a high BA incidence in boys was coincident with high total IgE levels, and that EA was associated with AD severity. Further studies focusing on these findings are of interest.

ACKNOWLEDGEMENTS
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REFERENCES