

Prevalence of Atopic Dermatitis and Serum IgE Values in Nursery School Children in Ishigaki Island, Okinawa, Japan

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Abstract

There have been many studies of the prevalence of atopic dermatitis (AD), but few population-based epidemiologic studies measure the prevalence in Japan among children aged 5 years and younger. We examined the prevalence of AD, serum total IgE levels and specific IgE antibodies to 10 common allergens among children in Ishigaki Island, Okinawa, Japan in 2001. We also obtained information on the predictability of the U.K. Working Party diagnostic questionnaire criteria for AD in this population. Five hundred and sixty five children aged 5 years and younger were enrolled in this study with informed consent from their parents. The questionnaire of the U.K. Working Party diagnostic criteria for AD was translated into Japanese, and the parents completed the questionnaire sheet. Physical examination and blood sampling were done for all children. Thirty-nine out of the 565 (6.9%) children were diagnosed with AD by physical examination. The total and specific IgE levels were significantly higher in the children with AD than in those without AD. High levels of total IgE were found in 33.3% of the children with AD. A specific IgE to one or more allergens was detected in 64.1% of children with AD. However, a substantial population of children without AD also had high levels of total IgE (12.7%) and a specific IgE to one or more allergens (30.2%), and the increment of total and specific IgE levels was significantly associated with age. The percentage of positive answers to the questionnaire of the U.K. Working Party diagnostic criteria for AD was significantly higher in children with AD (59.0%) than in children without AD (5.3%) ($P < 0.0001$). Its specificity was 94.7%. The false negative rate was 41%. In conclusion, the prevalence of AD was relatively low in children in Ishigaki Island. High levels of total IgE were found in only one third of children with AD under 5 years of age. The Japanese translated form of the questionnaire of the U.K. Working Party diagnostic criteria for AD should be refined to improve its sensitivity.

Abbreviation: AD; atopic dermatitis

Key words: atopic dermatitis; epidemiology; questionnaires; immunoglobulin E

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that is characterized by relapsing itch and eczema. It is a major skin disease of children that is increasing in both developed (1–3) and developing countries (4). A similar trend has been documented in Japan (5); however, one study has reported that AD is no longer increasing (6). There have been many studies of the prevalence of AD (6–13), but few population-based epidemiologic studies that measure the prevalence in Japan

Table 1. The prevalence of atopic dermatitis (AD) in children aged 5 years and under in nursery schools in Ishigaki City, Okinawa, Japan, in 2001

Age (years)	Boys		Girls		Total	
	Numbers examined	AD Cases (%)	Numbers examined	AD Cases (%)	Numbers examined	AD Cases (%)
1	47	2 (4.3)	41	4 (9.8)	88	6 (6.8)
2	57	3 (5.3)	56	3 (5.4)	113	6 (5.3)
3	78	5 (6.4)	52	8 (15.4)	130	13 (10.0)
4	65	5 (7.7)	68	4 (5.9)	133	9 (6.8)
5	55	4 (7.3)	46	1 (2.2)	101	5 (5.0)
Total	302	19 (6.3)	263	20 (7.6)	565	39 (6.9)

among children aged 5 years and younger.

The first set of standardized diagnostic criteria for AD arose from the work of Hanifin and Lobitz, and it was revised by Hanifin and Rajka (14, 15). The Japanese Dermatological Association criteria for the diagnosis of AD were established in 1995 (16). In order to set more useful criteria for mass-screening, the United Kingdom (U.K.) Working Party furthered the development of a standardized questionnaire defining the diagnostic criteria for AD (17). This questionnaire was composed of only 5 questions that were easy to answer by parents.

The aim of the present study was to determine the prevalence of AD, serum total IgE, and specific IgE antibodies among children aged 5 years and younger living in a relatively isolated area, Ishigaki Island. An additional aim of the study was to obtain information on the predictability of the questionnaire of the U.K. Working Party diagnostic criteria for AD when used in combination with physical examination in a Japanese population.

Methods

Study population

A large-population, long-term study of residents of the Yaeyama District of Okinawa, Japan for hepatitis B virus markers has been ongoing since 1968 (18–20). The present study was done as a part of the above-mentioned epidemiologic study in 2001. We visited 15 nursery schools in

Ishigaki Island, which has a population of 45,000, in the Yaeyama District of Okinawa Prefecture, Japan. Approval for the study was obtained from the Ethics Committee of Kyushu University Hospital as well as from the directors and class teachers of the schools. Informed consent to allow participation of the children was obtained from the parents and guardians. The yearly average temperature and humidity were 25.4°C and 76% on Ishigaki Island.

Six hundred and five children were originally enrolled in the study. There were 40 exclusions because of insufficient physical and laboratory examination or incomplete answers to questionnaires. The remaining 565 children were 302 boys and 263 girls, with a mean age of 3.1 years, and represented 13.7% of the 4,112 kindergarten pupils in Ishigaki City. Physical examinations with questionnaires concerning histories of symptoms and family history were completed, and venous blood samples were obtained between July 30 and August 3, 2001.

Physical and laboratory examination

The medical examinations for all children were done by two dermatologists from the Department of Dermatology at Kyushu University Hospital. AD was diagnosed according to the Japanese Dermatological Association criteria for the diagnosis of AD (16). All children were tested for total and specific IgE antibodies. Total IgE level was determined by a radioimmunoassay with a detection limit of 20 IU/ml (Shionoria IgE, Shionogi & Co., Ltd. Japan). A total IgE

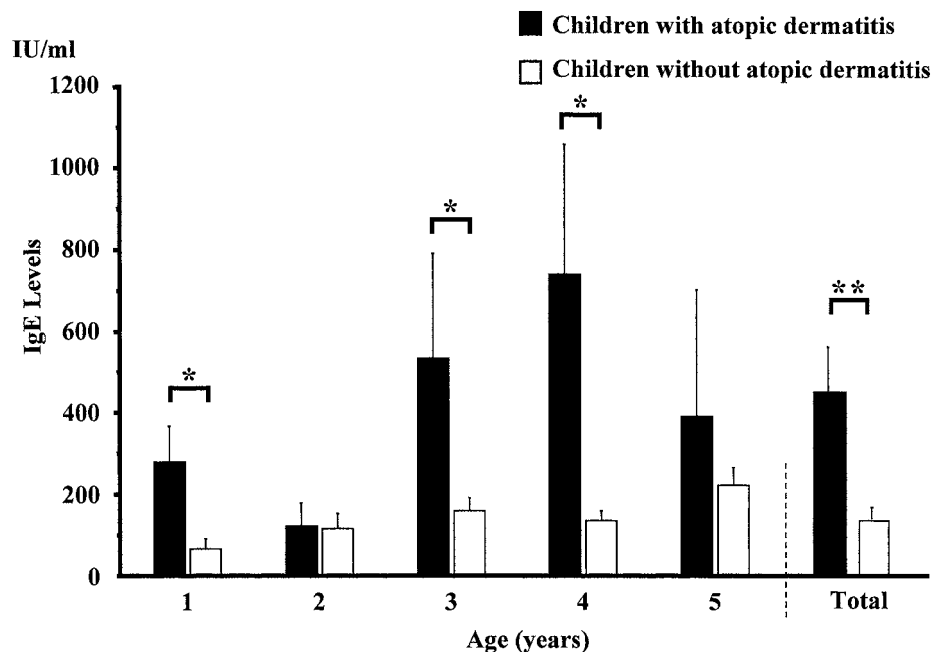


Fig. 1. Levels of total IgE in children 5 years of age and younger in nursery schools, Ishigaki City, Okinawa, Japan, in 2001.

The black bar (■) indicates children with AD and the open bar (□) shows children without AD. The standard deviations are shown by the thin, vertical bars and statistical significance is indicated by the “*” ($P<0.05$) and “**” ($P<0.001$).

Table 2. Comparison of the rates of abnormal total IgE levels between children with and without atopic dermatitis (AD) in Ishigaki City, Okinawa, Japan, in 2001

Age (years)	With AD		Without AD	
	No. tested	Abnormal IgE No. # (%)	No. tested	Abnormal IgE No. # (%)
1	6	3 (50.0)	82	3 (3.7)**
2	6	1 (16.7)	107	7 (6.5)**
3	13	3 (23.1)	117	23 (19.7)**
4	9	5 (55.6)	124	15 (12.1)**
5	5	1 (20.0)	96	19 (19.8)**
Total	39	13 (33.3)*	526	67 (12.7)

#A total IgE level of over 230 IU/ml was considered abnormal.

*A statistically significant difference was found between children with and without atopic dermatitis ($P=0.0029$)

** $P=0.0007$, calculated by use of the Cochran Armitage test.

level over 230 IU/ml was considered abnormal for statistical analysis. Specific IgE antibodies against aeroallergens such as house dust, Japan-

ese cedar pollen, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Candida*, *Malassezia*, and food allergens, such as chicken egg white,

Table 3. Comparison of positive specific IgE antibody responses of children in Ishigaki City, Okinawa, Japan, in 2001, with and without atopic dermatitis (AD)

Specific IgE antibody	AD children (n=39) Positive No. (%)	Non-AD children (n=526) Positive No. (%)	P value*
house dust	17 (43.6)	115 (21.9)	0.0038
Japanese cedar pollen	0 —	0 —	—
<i>D. pteronyssinus</i>	19 (48.7)	122 (23.2)	0.0008
<i>D. farinae</i>	19 (48.7)	98 (18.6)	<0.0001
<i>Candida</i>	2 (5.3)	2 (0.4)	0.0255
<i>Malassezia</i>	0 —	1 (0.2)	—
chicken egg white	10 (25.6)	57 (10.8)	0.0167
cow's milk	9 (23.1)	68 (12.9)	0.1233
rice	1 (2.6)	0 —	—
soy	2 (5.3)	2 (0.4)	0.0255
one or more antibodies	25 (64.1)	159 (30.2)	<0.0001

*P values represent the result of statistical comparison of children with and without atopic dermatitis.

D. pteronyssinus, *Dermatophagoides pteronyssinus*; *D. farinae*, *Dermatophagoides farinae*

Table 4. Comparison of positive rates for one or more specific IgE antibodies in children with and without atopic dermatitis (AD) in Ishigaki City, Okinawa, Japan, in 2001 by age

Age (years)	with AD		without AD	
	No. tested	Abnormal No. (%)	No. tested	Abnormal No. (%)
1	6	3 (50.0)	82	21 (27.6)**
2	6	5 (83.3)	107	29 (27.1)**
3	13	5 (38.5)	117	36 (30.8)**
4	9	9 (100.0)	124	32 (25.8)**
5	5	3 (60.0)	96	41 (42.7)**
Total	39	25 (64.1)*	526	159 (30.2)

*A statistically significant difference was found between children with and without atopic dermatitis (P<0.0001)

**P=0.0394, calculated by use of the Cochran Armitage test.

cow's milk, rice, and soy were tested with the Pharmacia Enzyme CAP procedure (Pharmacia CAP System Specific IgE FEIA, Pharmacia Diagnostics AB, Sweden). A level of specific IgE antibodies over 0.7 UA/ml was considered abnormal for statistical analysis.

Questionnaire

The questionnaire of The U.K. Working Party diagnostic criteria for AD was translated into

Japanese by a staff member of Kyushu University Hospital. The questionnaire has 5 questions regarding the present and past history of skin conditions (17). Each one-page questionnaire was completed by parents on behalf of their children. Children with suitable positive answers were diagnosed as AD using the same evaluation method proposed by the U.K. Working Party (17).

Table 5. Responses to the United Kingdom Working Party questionnaire for children with and without AD diagnosed by clinical examination

Questionnaire		Physical examination	
		AD N=39	Non-AD N=526
AD	N=51	23 (59%)	28 (5.3%)
Non-AD	N=514	16 (41%)	498 (94.7%)

Statistical analysis

Continuous data were expressed as mean values $\pm$ standard deviation (SD) or standard error (SE) of the mean. Unpaired t-test and Mann-Whitney U-test were used to compare the means of samples between the two groups. The chi-square test or Fisher's exact test was used for categorical variables for comparisons between the two groups. The Cochran-Armitage test was used to determine the relationship between the increase or decrease in the prevalence rate of AD or the IgE abnormality rate. $P < 0.05$ was considered statistically significant.

Results

Prevalence of AD

Table 1 shows the overall prevalence of AD in the study population. Out of 565 children, 39 (6.9%) were diagnosed with AD by physical examination. The prevalence peaked at age 3 (10%), and was lowest at age 5 (5%); however, the age-related difference was not statistically significant ($P = 0.7146$ by the Cochran-Armitage test). No significant differences were found when boys (19 of 302, 6.3%) and girls (28 of 263, 7.6%) were compared for disease prevalence.

Total IgE levels

The mean ($\pm$ SE) total IgE levels were significantly higher in children with AD (451.1 ± 120.4 IU/ml) than in those without AD (139.2 ± 14.7 IU/ml) ($P < 0.001$ by Mann-Whitney U-test) (Fig. 1). The total IgE levels were quite variable in each age group, and significant differences in mean IgE levels were found at ages 1, 3, and 4 between chil-

dren with and without AD (1 year old, $P = 0.0026$; 3 years old, $P = 0.0272$; and 4 years old, $P = 0.0037$, by Mann-Whitney U-test) (Fig. 1). As shown in Table 2, the occurrence of abnormal total IgE levels of over 230 IU/ml was significantly higher in children with AD (13 of 39, 33.3%) than in those without AD (67 of 526, 12.7%) ($P = 0.0029$ by the chi-square test). Interestingly, the rate of abnormal total IgE levels in children with AD did not significantly increase with age, however; the rate of abnormal total IgE levels in children without AD significantly increased with age ($P = 0.0007$ by the Cochran-Armitage test) (Table 2).

Positivity of specific IgE antibodies against aeroallergens and food allergens

Antigen-specific IgE antibodies against aeroallergens and food allergens, as indicated by values over 0.7 UA/ml, were found in 184 (32.6%) of the total of 565 children. Table 3 shows the differences in specific IgE antibody between children with and without AD. A positive response for one or more specific IgE antibodies was significantly higher in children with AD (64.1%) than in those without AD (30.2%) ($P < 0.0001$). Specific IgE antibody positivities, with the exceptions of Japanese cedar pollen, *Malassezia*, cow's milk and rice, were significantly higher in children with AD than those without AD (Table 3). The percentage positivity of specific IgE antibodies in children with AD did not significantly differ according to age (Table 4) (38.5% to 100%, $P = 0.3618$ by the Cochran-Armitage test). However, the percentage positivity of specif-

ic IgE antibodies significantly increased with age in children without AD (Table 4) (25.8% to 42.7%, $P=0.0394$ by the Cochran-Armitage test).

Questionnaire

We determined the sensitivity and specificity of the translated questionnaire of the U.K. Working Party diagnostic criteria for AD (Table 5). Fifty-one out of 565 children (9%) fulfilled the criteria for AD by the questionnaire. When compared to the actual diagnosis by physical examination, the sensitivity was 59% (23 out of 39), and the specificity was 94.7% (498 out of 526). The false positive and negative rates were 5.3% and 41%, respectively (Table 5).

Discussion

Symptoms of AD began during the first year of life in 65% of the children and in 85% during the first 5 years (21); it is thus worthwhile to determine the prevalence in children under the age of 5 years. In 2000 to 2002, the research team of the Japanese Ministry of Welfare (chief researcher; Dr. S. Yamamoto) performed physical examinations of 39,755 children living in Asahikawa, Iwate, Tokyo, Gifu, Osaka, Hiroshima, Kochi, and Fukuoka (22). They reported that the national average prevalence rate of AD was 12.8% in 4-month-old children, 9.8% in 18-month-old, 13.2% in 3-year-old, 11.8% in 6- to 7-year-old, and 10.6% in 11- to 12-year-old children. In our study, the prevalence of AD (6.9%) in children aged 5 years and younger in Ishigaki Island, which is located in the subtropical zone of Japan, was lower than the average rate on the mainland of Japan. It is also interesting that the present result, like Yamamoto's study, showed that the prevalence peaked at age 3. A worldwide survey has reported that AD is increasing in the developed countries in cooler climates (8). Japanese investigators also reported that the prevalence (17.3%) of AD was significantly higher in the cooler climate of Gifu than in the warmer climate of Itoman, Okinawa (3.4%), even after con-

trolling for genetic and environmental factors (9, 10). The reason for the lower prevalence in Okinawa (Itoman and Ishigaki) remains to be elucidated.

IgE levels have been reported to be elevated in 80 to 85% of children who developed AD (23, 24). In the present study, the total IgE levels were significantly higher in children with AD than in those without disease. The children with AD also had higher positive rates of most specific IgE antibodies against aeroallergens and food allergens than the children without AD. However, the positive percentage was lower than expected (high levels of total IgE; 33.3%, one or more specific IgE; 64.1%). None of the children had specific IgE antibody to Japanese cedar pollen, probably because there are no cedars in Ishigaki. Approximately 20% of children with AD have been reported to show allergic reactions to food constituents (25). In infancy allergic sensitization is predominantly to food. In later childhood, allergic sensitization to aeroallergens, such as house dust mites and pollen, is common (26). We also confirmed that the major allergens (specific IgE positive rates) were house dust mites, egg white, and milk in children with AD in Ishigaki. It should be emphasized that high serum levels of IgE were detected in 12.7% (67/526) of children without AD, and that 30.2% of these non-atopic children had one or more positive specific IgE antibodies to common allergens in our study. House dust mites, milk, and egg white were also the major antigens for specific IgE production even in the non-atopic children. It is also very interesting that both the total and specific IgE levels significantly increased with age in children without AD. The tendency of age-related accumulation of total and specific IgE was not observed in the children with AD, because it had already reached high levels as early as at age 1. Nolles et al. (27) reported a similar age-related increase of IgE antibodies. These results suggest (1) that the total and specific IgE levels increase with age probably with cumulative exposure to common al-

lergens even in non-atopic individuals, and (2) that earlier and higher increases in total and specific IgE antibodies are associated with AD.

The prevalence of AD has been studied in a variety of populations throughout the world (6–13), but comparisons of prevalence is difficult because of differences in study populations and study methods. Some investigators have measured point prevalence (28, 29), while others have measured 12 months prevalence in different age groups (8). The variation problem of study designs was addressed by the International Study for Asthma and Allergies in Childhood (ISAAC) (8). The methodology was subsequently standardized by the use of a questionnaire based on the U.K. Working Party definition of AD (17). A previous validity study suggested that the questionnaire might slightly overestimate the true prevalence (30). In the present study, we translated the questionnaire of the U.K. Working Party into Japanese and analyzed the sensitivity and specificity of the translated questionnaire. Although the specificity of the translated questionnaire for AD was 94.7%, its sensitivity was only 59%. This low sensitivity may be due to some incomprehensibility in the Japanese translation and to insufficient parent cooperation. It is critical that we refine the translation to improve the parents' understanding of the translated questionnaire.

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