

Atopic Dermatitis, Dry Skin and Serum IgE in Children in a Community in Japan

Takeshi Wakamori^a Norito Katoh^a Shinya Hirano^a Saburo Kishimoto^a
Kotaro Ozasa^b

Departments of ^aDermatology and ^bEpidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine Graduate School of Medical Sciences, Kyoto, Japan

Key Words

Atopic dermatitis · Dry skin · IgE · Prognosis · School children

Abstract

Background: Long-term, prospective studies investigating the prevalence, serum IgE and the natural history of atopic dermatitis (AD) in a community are lacking. **Methods:** In a Japanese community, the skin of primary school children and junior high school students was examined and a questionnaire was given to their parents; their serum total IgE, and house dust mite (HDM)- and Japanese cedar pollen (JCP)-specific IgE levels were also assessed once a year for 9 years. **Results:** The median AD prevalence in all students (492 in 1998 and 380 in 2004) was 7.6% (6.1–10.4%). The prevalence and the area of skin eruptions of AD decreased with growth. Serum total and HDM-specific IgE levels were high in AD patients, and significant differences were noted for both levels between children with and without later remission of skin eruptions at the time of primary school entry. IgE level increases were noted in the following order: healthy skin < dry skin < AD. In children presenting only with dry skin without atopic disorders, such as AD, asthma and allergic rhinitis, levels of total HDM- and JCP-specific IgE were significantly higher than in children with healthy skin. **Conclusions:** The infantile IgE level serves as a prognostic index,

and sensitization to inhalant allergens may be easily established in individuals with clinically dry skin, even when AD is not present, and this may lead to the development of atopic disorders.

Copyright © 2009 S. Karger AG, Basel

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with relapsing pruritic eczema. A genetic background leading to epidermal barrier dysfunction [1, 2] and atopic diathesis [3, 4] is believed to be the main cause of AD, but many cases heal in the infantile phase and improvement around puberty is common [5–7]. Most epidemiological studies have shown that the prevalence of AD has increased over recent decades [8–24]. However, studies on AD prevalence are often cross-sectional in a certain area, and studies on the natural history of AD have been performed in hospital-confirmed cases. Fewer studies have examined changes in prevalence in a community, and long-term, prospective studies on the natural history of AD in a community are lacking.

In AD, the levels of total and specific IgE against inhalant allergens, e.g. house dust mite (HDM) and Japanese cedar pollen (JCP), are often increased [3, 7]. AD is

also associated with epidermal barrier dysfunction, resulting in increased transepidermal water loss and clinically dry skin. Sweat, irritant agents such as detergents and allergens easily enter the body via dry skin, and this is considered to be associated with the development and progression of eczema [1]. Allergens entering the body via dry skin may also be associated with the progression of other atopic disorders, e.g. asthma and allergic rhinitis, a process referred to as 'atopic march' [25]. Information regarding IgE level changes in children with AD and in healthy children is important to elucidate the mechanisms of atopic march, but few studies have investigated this issue [26]. Moreover, data on total, and HDM- and JCP-specific IgE levels in children with clinically dry skin but no AD or other atopic disorder have not been reported in the literature.

In a Japanese community, the skin of primary school children and junior high school students was examined over a 9-year period, and changes in the prevalence of AD, area of skin eruptions, and total and HDM- and JCP-specific IgE levels as well as IgE levels in children with dry skin and patients with AD were investigated.

Patients and Methods

Study Population

A long-term epidemiological study on the prevalence of seasonal allergic rhinitis against JCP in primary school children (6–11 years of age) and junior high school students (12–14 years of age) was initiated in 1993 in a rural community (population of around 6,000 in 1995 to 5,400 in 2004), Kyoto Prefecture, Japan, as reported previously [27–29]. We joined this epidemiological study in 1996 and performed skin examinations such as inspection and palpation. There is one public primary school and one junior high school in this town (total number of students: 586 in 1996 and 395 in 2004). Children move in or out of the town only rarely and most enter primary school and go on to junior high school. The study was approved by the Ethical Committee of the Kyoto Prefectural University of Medicine, and written informed consent was obtained from all parents.

Skin Examination and Blood Sampling

All children underwent a skin examination performed by a dermatological specialist (T.W.) once a year in May from 1996 to 2004 (9 years). The dermatologist visited the health care rooms of the schools to perform this examination. Diagnosis of AD was based on the diagnostic criteria of the UK working party for AD [30] and included an itchy skin condition (or parental report of scratching or rubbing) and at least three of the following criteria: (1) a history of involvement of skin creases, e.g. the folds of the elbows, behind the knees, the fronts of the ankles or around the neck, or the cheeks in children under 10; (2) a personal history of asthma or hay fever (or a history of atopic disease in a first-degree relative in children under 4); (3) a history of a general dry skin in

the last year; (4) visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4), and (5) onset under the age of 2 (not used in children under 4). Dry skin was defined as skin not having an inflamed skin condition but having xerosis, i.e. a condition of rough, dry skin with fine scaling of skin [31]: the subject was diagnosed with dry skin if no eczema was evident on inspection and palpation, and if the subject had no history of eczema from birth based on a questionnaire mentioned below. Skin without these abnormalities was regarded as healthy. Users of emollients accounted for less than 1% of all subjects based on the questionnaire described below, and these subjects were excluded from statistical analysis. None of the children/students had received specific immunotherapy against HDM or JCP. The percent area of AD skin eruptions in the whole body was calculated using the rule of nine in adults and older children in extent criteria of the severity Scoring of Atopic Dermatitis (SCORAD index) [32]. Since examinations were performed only in the health care rooms of schools where airflow, room temperature or humidity were not controllable, hydration of the stratum corneum and transepidermal water loss were not measured. Subjects with ichthyosis were not excluded from analysis, and since this condition may cause the development of dry skin from childhood it is possible that cases of ichthyosis were included in the AD or dry skin groups.

Venous blood was collected from almost all subjects immediately after the skin examination, and the serum total IgE, HDM (Der p1)-specific IgE and JCP-specific IgE (CAP-RAST system; Pharmacia, Uppsala, Sweden) were measured. A skin prick test was not performed.

Questionnaire

A questionnaire was given to the parents in addition to the skin examination each year. The questionnaire consisted of three questions about the current and past skin conditions, and required a 'yes' or 'no' answer to the following questions: (1) Has a doctor ever pointed out that your child has atopic dermatitis? (2) Has your child had a history of involvement of skin creases, e.g. such as the folds of elbows, behind the knees, the fronts of the ankles or around the neck? (3) Has your child had a history of a general dry skin in the last year? Similar questions on the medical history of asthma, urticaria, rhinitis and conjunctivitis were also asked, and information on the use of emollients and a family history of atopic disorders (e.g. AD, asthma and allergic rhinitis in the parents) was obtained.

Statistical Analysis

Data were expressed as means $\pm$ SD (fig. 3; tables 1, 2) and as means $\pm$ SEM (fig. 4, 5). The Mann-Whitney U test was employed to compare IgE levels between improvement with growth and no improvement with growth investigated individually in children with AD (fig. 5). Fisher's protected least significant difference test was used to compare IgE levels in subjects with dry skin and AD using log-transformed values (tables 1, 2). Contingency tables were used to compare complications (table 1) and family history of allergic disorders (table 2) for subjects with dry skin and AD. All statistical analyses were assessed using StatView (version 5; SAS Institute, Cary, N.C., USA) on a Macintosh computer. $p < 0.05$ was considered statistically significant.

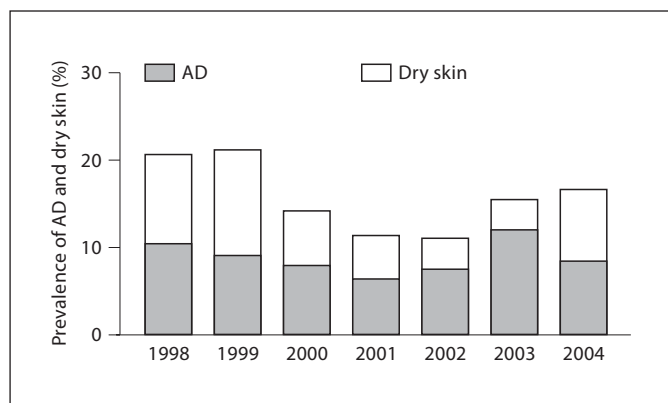


Fig. 1. The prevalence of AD and dry skin in all students for 7 years (from 1998 to 2004).

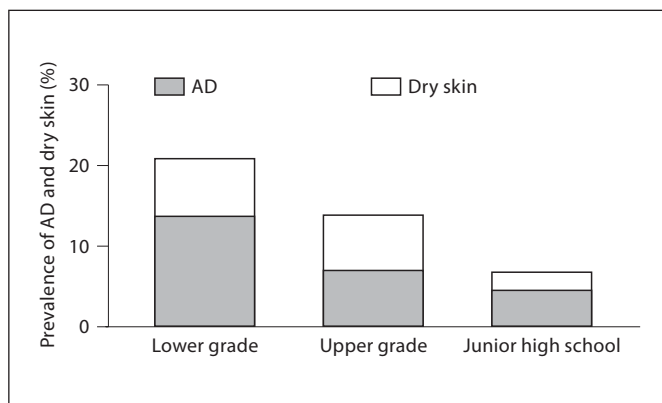


Fig. 2. Changes in the prevalence of AD and dry skin with growth investigated in children in the 1st–3rd grade (lower grade) of primary school in 1998, who attended the 4th–6th grade (upper grade) of primary school in 2001 and junior high school in 2004.

Results

Number of Students and the Prevalence of AD and Dry Skin

The total number of subjects was 586 in the 1st year of the survey, 1996, and gradually decreased to 395 in 2004, reflecting the declining total and younger population in rural areas of Japan. Sex ratios (boys/girls) ranged from 0.88 to 1.03.

As shown in figure 1, the median, minimum and maximum prevalence values for AD were 7.6 (2002), 6.1 (2001) and 10.4% (2003), respectively, in all students (492 in 1998 and 380 in 2004). The median, minimum and maximum prevalence values of dry skin were 6.3 (2004), 1.7 (2002) and 13.9% (1999), respectively.

The prevalence of AD was 11.6% in 1st- to 3rd-grade (lower-grade) primary school children in 1998. In 4th- to 6th-grade (upper-grade) primary school children, the prevalence was 6.7% in 2001. It was 5.1% in junior high school students in 2004 (fig. 2). A similar tendency to a reduction in the prevalence of AD with growth was noted every year. The prevalence of dry skin similarly decreased as the children grew.

Changes in growth in the area of skin eruptions of AD were investigated during a 7-year period in the 165 children who entered primary school between 1996 and 1998 (68 in 1996, 42 in 1997 and 55 in 1998), and this investigation was performed every year until they attended 1st-grade junior high school. As shown in figure 3, the percentage of the area of AD skin eruptions in the whole body decreased with growth in 26 children with AD (11

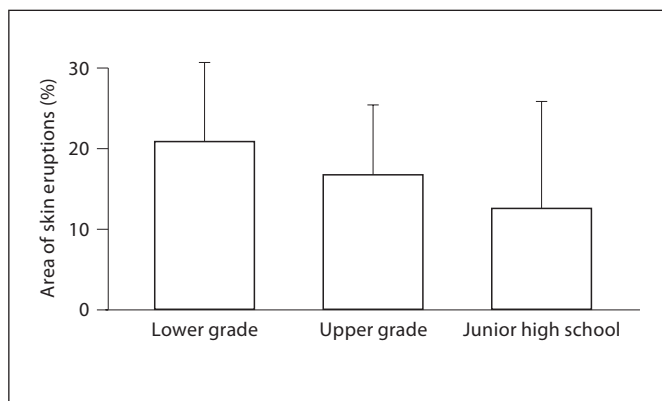


Fig. 3. Changes with growth in the area of skin eruptions of 26 AD children. This investigation was performed every year for 7 years in children who entered primary school between 1996 and 1998 (11 in 1996, 5 in 1997 and 10 in 1998) and later attended the 4th–6th grade (upper grade) of primary school and junior high school. Means $\pm$ SD.

in 1996, 5 in 1997 and 10 in 1998). The mean percentage was 20.0% in lower-grade primary school children, decreased to 15.9% in upper-grade primary school children and further decreased to 11.0% at the time of entry into junior high school.

Skin Eruptions and IgE Levels

In order to investigate the natural history of AD and prognostic factors further, we analyzed the changes in the area of skin eruptions every year for 7 years indi-

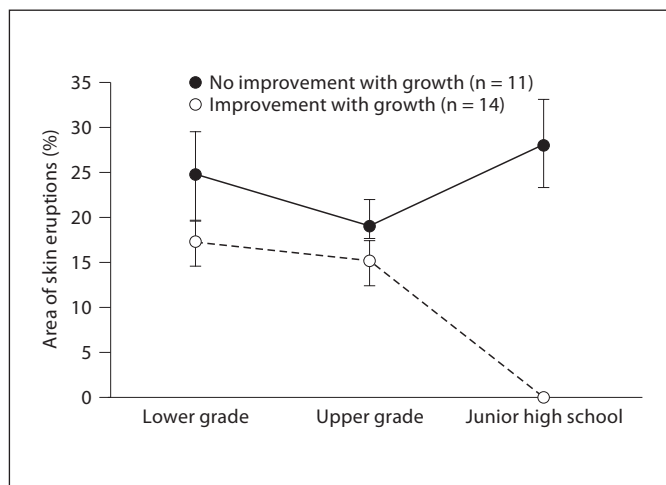


Fig. 4. Changes with growth in the area of skin eruptions investigated individually in 25 AD children who entered primary school between 1996 and 1998. This investigation was performed every year for 7 years from the 1st–3rd grade (lower grade) to the 4th–6th grade (upper grade) of primary school and to the 1st grade of junior high school. Means $\pm$ SEM. Occasionally, error bars are left out to avoid confusion.

vidually in 25 children with AD who entered primary school between 1996 and 1998 until they attended 1st-grade junior high school. As shown in figure 4, skin eruptions were noted from the 1st to 6th grade and then disappeared at the time of entry into junior high school in 14 of the 25 children (56.0%; group 1, improvement with growth). In the other 11 children (44.0%), skin eruptions were noted even at the time of entry into junior high school (group 2, no improvement with growth). In group 1, the mean percent area of skin eruptions was 17.4% in the 1st to 3rd grade, and 14.8% in the 4th to 6th grade. In group 2, it was 24.0% in the 1st to 3rd grade, 17.2% in the 4th to 6th grade and 24.5% at the time of entry into junior high school. The area of skin eruptions in group 2 was larger than in group 1 throughout the study period.

At the time of primary school entry, the total IgE (fig. 5a) and the HDM-specific IgE levels (fig. 5b) were significantly higher in group 2 than in group 1 (total IgE: $p = 0.0060$, and HDM-specific IgE: $p = 0.0089$), but there was no significant difference in the JCP-specific IgE level

Table 1. Serum total, and HDM- and JCP-specific IgE levels and respiratory allergies in subjects with dry skin and AD

Subjects	n	Total IgE IU/ml	HDM-specific IgE UA/ml	JCP-specific IgE UA/ml	Asthma %	Allergic rhinitis, %
Healthy skin (HS)	328	192.4 $\pm$ 480.9	16.5 $\pm$ 70.2	13.9 $\pm$ 50.1	4.7	27.5
Dry skin (DS)	41	376.5 $\pm$ 727.4	32.9 $\pm$ 95.3	23.4 $\pm$ 68.9	9.5	28.6
Atopic dermatitis (AD)	44	1,011.1 $\pm$ 2,004.9	68.8 $\pm$ 119.1	25.5 $\pm$ 57.7	14.3	45.2
Total	413					
Statistical significance						
HS:DS		$p = 0.0161$	$p = 0.0140$	$p = 0.2915$	$p = 0.2572$	$p = 0.8553$
HS:AD		$p < 0.0001$	$p < 0.0001$	$p = 0.0007$	$p = 0.0268$	$p = 0.0288$
DS:AD		$p = 0.0150$	$p = 0.0301$	$p = 0.0845$	$p = 0.7379$	$p = 0.1745$

Table 2. Serum total, and HDM- and JCP-specific IgE levels and family history of atopic disorders in subjects with dry skin without atopic disorders

Subjects	n	Total IgE IU/ml	HDM-specific IgE UA/ml	JCP-specific IgE UA/ml	Family history, %		
					AD	asthma	allergic rhinitis
Healthy skin	66	60.6 $\pm$ 83.0	5.1 $\pm$ 17.0	0.7 $\pm$ 1.5	2.9	8.6	17.1
Dry skin	23	174.3 $\pm$ 244.2	18.3 $\pm$ 33.7	3.5 $\pm$ 7.5	16.7	10.0	13.3
Total	89						
Statistical significance		$p = 0.0181$	$p = 0.0392$	$p = 0.0025$	$p = 0.0242$	$p > 0.9999$	$p = 0.7709$

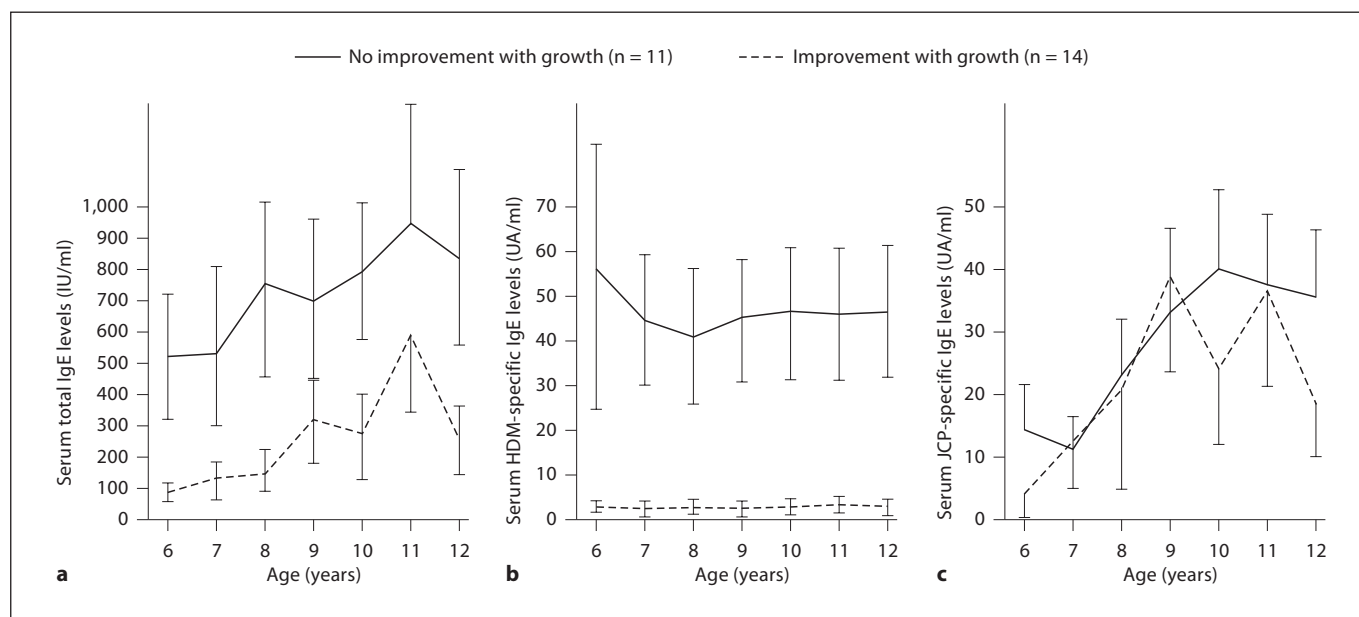


Fig. 5. Changes with growth in the serum levels of total IgE (a), HDM-specific IgE (b) and JCP-specific IgE (c) investigated individually in children with AD. Means $\pm$ SEM. Occasionally, error bars are only depicted on one side to avoid confusion.

between the two groups (fig. 5c). Based on these findings, total and HDM-specific IgE levels at the time of primary school entry may serve as indices for the prognosis of AD.

IgE Levels in Subjects with Dry Skin and AD

IgE is considered to be involved in the pathogenesis of extrinsic-type AD. In addition, IgE also contributes to the atopic march. Therefore, serum total and HDM- and JCP-specific IgE levels were analyzed in all children and students. As an example, the data obtained in 1998 (413 subjects) are listed in table 1 (healthy skin: 328; dry skin: 41, and AD: 44). IgE levels and rates of complication by atopic disorders such as asthma and allergic rhinitis increased in the following order in subjects: healthy skin < dry skin < AD. Significant differences in total and HDM-specific IgE levels were present among these groups. Similar findings were obtained in the other years.

Since the IgE level also increases in other atopic disorders, e.g. asthma and allergic rhinitis, we analyzed the IgE levels in children with clinically dry skin alone without atopic disorders. In 89 children who entered primary school between 1998 and 2000 (33 in 1998, 27 in 1999 and 29 in 2000) without atopic disorders such as AD, asthma, urticaria, allergic rhinitis and allergic conjunctivitis, the levels of IgE increased in the order of healthy skin < dry

skin (table 2). Levels of total, and HDM- and JCP-specific IgE and family history of AD differed significantly between subjects with healthy skin and those with dry skin. Similar findings were observed throughout the study period (1996–2004). Thirteen children were followed for 5 years until they were 6th-year pupils in 2003–2005, and 7.7 (1/13) and 38.5% (5/13) developed AD and allergic rhinitis, respectively.

Discussion

There are many studies on the prevalence of childhood AD worldwide [8–24], and the mean prevalence appears to be approximately 10% in industrial countries. A similar prevalence of AD was obtained in our 9-year survey in primary school children and junior high school students. There is widespread belief that AD and other atopic disorders have been increasing over recent decades, but the prevalence of AD did not change markedly during the 9-year period in the community studied. Reasons proposed for an increase in AD include increased exposure to diesel exhaust particles due to urbanization and lifestyle changes, including air-conditioned indoor living and increased bathing frequency and soap consumption. The community investigated in the current

study is a rural town that has retained a non-urbanized environment, and this may be the reason for the absence of changes in the prevalence of AD over 9 years.

The natural history of AD in a community setting has not been studied extensively, but available reports suggest that AD with childhood onset is commonly a relapsing disease with a clearance rate of 50–70% after 10 years and remission around puberty [5, 6]. In the current study, the prevalence of AD decreased with growth and the prevalence at the time of junior high school entry was about half that in lower-grade primary school children. The percentage of the area of whole-body AD skin eruptions also decreased with growth. These changes may be due to growth-related strengthening of the epidermal barrier function against water loss through increased secretion of sebum covering the corneal layer [33].

The area of skin eruptions in lower-grade primary school children was larger in children in whom skin eruption due to AD persisted in junior high school compared with those in whom skin eruption remitted in junior high school. The area of skin eruptions in lower-grade primary school children exceeded 20% in many children in whom skin eruptions persisted in junior high school. For children with eczema in regions with a high prevalence of AD, such as the neck, glenoid cavities and intertriginous areas of the extremities, the area of skin eruptions was about 9% [32]. With more widely expanded eczema, it is very likely that eczema will persist in pubescence.

The concept of the atopic eczema/dermatitis syndrome (AEDS) has recently been proposed [34–36]. AEDS is classified into allergic AEDS (also referred to as intrinsic AD) and non-allergic AEDS (extrinsic AD). We investigated changes in the IgE level with regard to the prognosis of AD skin eruptions. The IgE level was high in the AD group with no improvement in skin eruptions, showing a similarity to allergic AEDS, whereas the IgE level was low in the AD group with improvement in skin eruptions, similarly to non-allergic AEDS. Approximately 80% of patients with AD show increased values of total IgE and/or specific IgE against food allergens as infants, and environmental allergens as children and adults [3, 7]. Allergic inflammation provoked by these allergens plays an important role in the pathogenesis of allergic AEDS [7], and a correlation between high IgE levels and the severity of symptoms has also been reported in AD patients [37, 38]. In the current study, the IgE level was high in AD patients, and significant differences were noted in the serum total and HDM-specific IgE levels at the time of primary school entry between children with and without

later remission of skin eruptions, suggesting that the infantile IgE level serves as a prognostic index. In addition, our results suggest that HDM allergy plays an important role in the pathogenesis of pediatric AD. Moreover, the serum total and JCP-specific IgE levels remained increased in junior high school students, even in those with AD remission with growth, indicating that patients less commonly ‘outgrow’ allergy. Wuethrich and Schmid-Grendelmeier [34] investigated the prevalence of AEDS in children 10–12 years of age who had already presented with AEDS at 2–4 years of age and found rates of allergic and non-allergic AEDS of 73.3 (11/15) and 57.1% (4/7), respectively, suggesting an association of IgE-mediated allergy with aggravation of AD to an intractable state. This association was also found in our study.

It is generally accepted that epidermal barrier dysfunction plays an essential role in the pathogenesis of AD [1]. Dry skin associated with epidermal barrier dysfunction allows irritant agents and inhalant allergens to enter the body, and antigen-specific and non-specific inflammation occurs easily. Langerhans cell activation [39] and increases in the levels of IgE-producing Th2 cytokines, such as IL-4 and IL-13, have been noted in skin showing epidermal barrier dysfunction [40], thus leading to allergic inflammation accompanied by Th2 cell activation [41, 42]. A relationship between the filaggrin gene and AD has recently been reported, and ichthyosis was shown to be complicated by asthma. This is of interest with regard to the relationship between epidermal barrier dysfunction and atopic march [2, 43]. On the other hand, the presence of reduced epidermal barrier function in individuals with xerosis without clinical inflammation has been reported [31]. Taken together, individuals with dry skin alone (i.e. without AD) may also be easily sensitized to environmental allergens. However, to our knowledge, there has been no previous report on IgE levels in individuals with dry skin alone without eczema.

In the current study, we investigated IgE levels in young subjects with xerosis alone without previous eczema or complication by asthma, urticaria, allergic rhinitis and conjunctivitis based on skin examination and a questionnaire answered by parents. The serum total and HDM- and JCP-specific IgE levels were significantly higher in subjects with clinically dry skin alone, with no history of atopy or eczema, than in healthy subjects. Five years later, AD and allergic rhinitis had developed in the subjects with dry skin and they were at increased risk of developing atopic disorders. Based on these findings, sensitization to inhalant allergens may be easily established in individuals with clinically dry skin, even when

AD is not present, and this may lead to the development of other atopic disorders, including asthma. Of note, the report on the filaggrin gene and AD was not available at the time of our study, and thus we did not compare filaggrin mutations and ichthyosis in children with AD and those with dry skin only.

Prevention management may reduce sensitization to inhalant allergens and progression of the atopic march [1]. We have initiated a prospective study to determine whether skin care for dry skin from infancy prevents elevation of IgE levels and the development of atopic disorders, with emphasis on avoidance of excessive air-conditioning, proper bathing habits (e.g. without scrubbing the body) and the use of moisture-rich skin care for all children with AD, dry skin and healthy skin.

Acknowledgments

The authors thank Prof. H. Takenaka, Department of Otorhinolaryngology (Osaka Medical College), for the measurement of serum IgE levels, and Prof. Y. Hisa, Dr. K. Dejima, and Dr. T. Hama (Department of Otorhinolaryngology-Head and Neck Surgery, Kyoto Prefectural University of Medicine Graduate School of Medical Sciences, Kyoto, Japan; Dr. K. Dejima is currently in the Kyoto Second Red Cross Hospital). This work was supported in part by Health and Labor Science Research Grants for Research on Allergic Disease and Immunology from the Ministry of Health, Labor and Welfare of Japan, and Grants-in-Aid for Scientific Research (Nos. 08670448, 11670382, 13670380, 16590510 and 18590608) from the Ministry of Education, Science, Culture and Sports of Japan.

References

- ▶ 1 Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, Duff GW, Ward SJ, Tazi-Ahnini R: New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *J Allergy Clin Immunol* 2006;118:3–21.
- ▶ 2 Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, Goudie DR, Sandilands A, Campbell LE, Smith FJ, O'Regan GM, Watson RM, Cecil JE, Bale SJ, Compton JG, DiGiovanna JJ, Fleckman P, Lewis-Jones S, Arseculeratne G, Sergeant A, Munro CS, El Houate B, McElreavey K, Halkjaer LB, Bisgaard H, Mukhopadhyay S, McLean WH: Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441–446.
- ▶ 3 Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA: New insights into atopic dermatitis. *J Clin Invest* 2004;113:651–657.
- ▶ 4 Hoffjan S, Epplen JT: The genetics of atopic dermatitis: recent findings and future options. *J Mol Med* 2005;83:682–692.
- 5 Vickers CFH: The natural history of atopic eczema. *Acta Derm Venereol* 1980;92:113–115.
- ▶ 6 Williams HC, Strachan DP: The natural history of childhood eczema: observations from the British 1958 birth cohort study. *Br J Dermatol* 1998;139:834–839.
- ▶ 7 Leung DY, Bieber T: Atopic dermatitis. *Lancet* 2003;361:151–160.
- ▶ 8 Kuhnyar A, Egyud K, Szabo I, Hunyadi J, Kosa L: Prevalence of atopic dermatitis among children under 19 in an East-Hungarian agricultural county. *Clin Dev Immunol* 2006;13:395–399.
- ▶ 9 Ellison JA, Patel L, Kecojevic T, Foster PJ, David TJ, Clayton PE: Pattern of growth and adiposity from infancy to adulthood in atopic dermatitis. *Br J Dermatol* 2006;155:532–538.
- ▶ 10 Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, Masi M: Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006;55:765–771.
- ▶ 11 Purvis DJ, Thompson JM, Clark PM, Robinson E, Black PN, Wild CJ, Mitchell EA: Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. *Br J Dermatol* 2005;152:742–749.
- ▶ 12 Darsow U, Laifaoui J, Kerschenlohr K, Wollenberg A, Przybilla B, Wuthrich B, Borelli S Jr, Giusti F, Seidenari S, Drzimalla K, Simon D, Disch R, Borelli S, Devillers AC, Oranje AP, De Raeve L, Hachem JP, Dangoisse C, Blondeel A, Song M, Breuer K, Wulf A, Werfel T, Roul S, Taieb A, Bolhaar S, Bruijnzeel-Koomen C, Bronnimann M, Braathen LR, Didierlaurent A, Andre C, Ring J: The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy* 2004;59:1318–1325.
- ▶ 13 Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, Wahn U; Multicenter Allergy Study Group: The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113:925–931.
- ▶ 14 Halken S: Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. *Pediatr Allergy Immunol* 2004;15:9–32.
- ▶ 15 Mortz CG, Lauritsen JM, Andersen KE, Bindslev-Jensen C: Type I sensitization in adolescents: prevalence and association with atopic dermatitis. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). *Acta Derm Venereol* 2003;83:194–201.
- ▶ 16 Girolomoni G, Abeni D, Masini C, Sera F, Ayala F, Belloni-Fortina A, Bonifazi E, Fabbrì P, Gelmetti C, Monfrecola G, Peserico A, Seidenari S, Giannetti A: The epidemiology of atopic dermatitis in Italian schoolchildren. *Allergy* 2003;58:420–425.
- ▶ 17 Smith-Sivertsen T, Tschachtchine V, Lund E: Atopy in Norwegian and Russian adults: a population-based study from the common border area. *Allergy* 2003;58:357–362.
- ▶ 18 Krause T, Koch A, Friborg J, Poulsen LK, Kristensen B, Melbye M: Frequency of atopy in the Arctic in 1987 and 1998. *Lancet* 2002;360:691–692.
- ▶ 19 Tay YK, Kong KH, Khoo L, Goh CL, Giam YC: The prevalence and descriptive epidemiology of atopic dermatitis in Singapore school children. *Br J Dermatol* 2002;146:101–106.
- ▶ 20 Gustafsson D, Sjöberg O, Foucard T: Development of allergies and asthma in infants and young children with atopic dermatitis – a prospective follow-up to 7 years of age. *Allergy* 2000;55:240–245.
- ▶ 21 Williams H, Robertson C, Stewart A, Khaled N, Anabwani G, Anderson R, Asher I, Beasley R, Bjoerksten B, Burr M, Clayton T, Crane J, Ellwood P, Keil U, Lai C, Mallol J, Martinez F, Mitchell E, Montefort S, Pearce N, Shah J, Sibbald B, Strachan D, von Mutius E, Weiland SK: Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999;103:125–138.

- ▶ 22 Patel L, Clayton PE, Addison GM, Price DA, David TJ: Linear growth in prepubertal children with atopic dermatitis. *Arch Dis Child* 1998;79:169–172.
- ▶ 23 Schultz LF, Diepgen T, Svensson A: The occurrence of atopic dermatitis in north Europe: an international questionnaire study. *J Am Acad Dermatol* 1996;34:760–764.
- ▶ 24 Williams HC: Is the prevalence of atopic dermatitis increasing? *Clin Exp Dermatol* 1992; 17:385–391.
- ▶ 25 Spergel JM, Paller AS: Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112:18–27.
- ▶ 26 Nickel R, Illi S, Lau S, Sommerfeld C, Bergmann R, Kamin W, Forster J, Schuster A, Niggemann B, Wahn U: Variability of total serum immunoglobulin E levels from birth to the age of 10 years. A prospective evaluation in a large birth cohort (German Multi-center Allergy Study). *Clin Exp Allergy* 2005; 35:619–623.
- ▶ 27 Ozasa K, Dejima K, Watanabe Y, Takenaka H: A longitudinal observation of sensitization to Japanese cedar pollen and house dust mite among schoolchildren. *Allergol Int* 1999;48:69–78.
- ▶ 28 Ozasa K, Dejima K, Hama T, Watanabe Y, Takenaka H: Exposure to Japanese cedar pollen in early life and subsequent sensitization to Japanese cedar pollen. *J Epidemiol* 2000;10:42–47.
- ▶ 29 Ozasa K, Dejima K, Takenaka H: Prevalence of Japanese cedar pollinosis among schoolchildren in Japan. *Int Arch Allergy Immunol* 2002;128:165–167.
- ▶ 30 Williams HC, Burney PG, Pembroke AC, Hay RJ: The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994;131:406–416.
- ▶ 31 Suehiro M, Hirano S, Ikenaga K, Katoh N, Yasuno H, Kishimoto S: Characteristics of skin surface morphology and transepidermal water loss in clinically normal-appearing skin of patients with atopic dermatitis: a video-microscopy study. *J Dermatol* 2004; 31:78–85.
- ▶ 32 Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A: Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997;195: 10–19.
- ▶ 33 Zouboulis CC: Acne and sebaceous gland function. *Clin Dermatol* 2004;22:360–366.
- ▶ 34 Wuethrich B, Schmid-Grendelmeier P: Natural course of AEDS. *Allergy* 2002;57:267–268.
- ▶ 35 Wuethrich B, Schmid-Grendelmeier P: The atopic eczema/dermatitis syndrome. Epidemiology, natural course, and immunology of the IgE-associated ('extrinsic') and the non-allergic ('intrinsic') AEDS. *J Invest Allergol Clin Immunol* 2003;13:1–5.
- ▶ 36 Wuethrich B, Cozzio A, Roll A, Senti G, Kundig T, Schmid-Grendelmeier P: Atopic eczema: genetics or environment? *Ann Agric Environ Med* 2007;14:195–201.
- ▶ 37 Johnson EE, Irons JS, Patterson R, Roberts M: Serum IgE concentration in atopic dermatitis. Relationship to severity of disease and presence of atopic respiratory disease. *J Allergy Clin Immunol* 1974;54:94–99.
- ▶ 38 Sampson HA: Jerome Glaser lectureship. The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 1988;81:635–645.
- ▶ 39 Katoh N, Hirano S, Kishimoto S, Yasuno H: Acute cutaneous barrier perturbation induces maturation of Langerhans' cells in hairless mice. *Acta Derm Venereol* 1997;77:365–369.
- ▶ 40 Hamid Q, Boguniewicz M, Leung DY: Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest* 1994;94:870–876.
- ▶ 41 Spergel JM, Mizoguchi E, Brewer JP, Martin TR, Bhan AK, Geha RS: Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. *J Clin Invest* 1998;101:1614–1622.
- ▶ 42 Kondo H, Ichikawa Y, Imokawa G: Percutaneous sensitization with allergens through barrier-disrupted skin elicits a Th2-dominant cytokine response. *Eur J Immunol* 1998;28:769–779.
- ▶ 43 Irvine AD, McLean WH: Breaking the (un)sound barrier: filaggrin is a major gene for atopic dermatitis. *J Invest Dermatol* 2006; 126:1200–1202.