Acta Derm Venereol 2015; 95: 480–484

CLINICAL REPORT

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

Satoshi TAKEUCHI[1,2], Hitokazu ESAKI[1], Norihiro FURUSYO[3,4], Sayaka HAYASHIDA[1], Kazuhiko YAMAMURA[1], Gaku TSUJI[1], Masaki TAKEMURA[1], Jun HAYASHI[3,4] and Masutaka FURUE[1]

Departments of Dermatology, [1]Graduate School of Medical Sciences, Kyushu University and [2]Federation of National Public Service Personnel Mutual Aid Associations, Hamanomachi Hospital, Fukuoka, [3]Department of General Internal Medicine, Kyushu University Hospital, and [4]Department of Environmental Medicine and Infectious Disease, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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.***

Accepted Oct 27, 2014; Epub ahead of print Oct 28, 2014

Acta Derm Venereol 2015; 95: 480–484.

Satoshi Takeuchi, Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan, E-mail: takeuchs@dermatol.med.kyushu-u.ac.jp

Atopic dermatitis (AD) is a common, chronically relapsing, severely pruritic, eczematous skin disease. The incidence of AD, including that of adolescent- and adult-type AD, is increasing worldwide (1–4). The aetiology and pathogenesis of AD are not fully understood; however, recent studies suggest that AD involves a complex interaction of skin barrier dysfunction, exposure to external allergens or microbes, a Th2-prone response, and psychosomatic reactions. Intense itching, sleep disturbance, appearance of severely affected skin, and other atopic symptoms impose a remarkable burden on affected individuals, their families, and society (5).

In 2001, we initiated a population cohort study that included nursery school children aged ≤6 years from Ishigaki Island, Okinawa, Japan; this study was named the Kyushu University Ishigaki Atopic Dermatitis Study (KIDS). Through the cohort study, we reported AD prevalence, serum total immunoglobulin E (IgE) and thymus and activation-regulated chemokine (TARC) levels, the spontaneous regression ratio, risk factors for AD, and the relationship between skin infections and childhood AD (6–9). In the present study, we report an update from the KIDS cohort on the dermatologist-examined AD prevalence and questionnaire-based incidence of AD and other related allergic diseases, risk factors for AD, serum total IgE and TARC levels, and factors other than AD that affect disease severity.

METHODS

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 immunosorbent assay (ELISA, Shionogi & Co., Ltd., Osaka, Japan), according to the manufacturer's protocols. Serum total

 doi: 10.2340/00015555-1989
 ISSN 0001-5555

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 χ^2-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 examinees' 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 SI[1]).

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 SII[1]).

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

	Boys		Girls		
	No *n*	Yes *n* (%[a])	No *n*	Yes *n* (%)	*p*-values χ^2-test
Atopic dermatitis	571	87 (13.2)	460	77 (14.3)	0.524
Allergic rhinitis	632	20 (3.1)	517	13 (2.5)	0.524
Bronchial asthma	536	113 (17.4)	466	63 (11.9)	0.008
Egg allergy	614	34 (5.3)	508	20 (3.8)	0.234

[a]% of total number of children.

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

	AD		Non-AD		
	No *n*	Yes *n* (%[a])	No *n*	Yes *n* (%)	*p*-values χ^2-test
Allergic rhinitis	154	9 (5.5)	995	24 (2.4)	0.036[b]
Bronchial asthma	115	45 (28.1)	887	131 (12.9)	0.00000
Egg allergy	122	30 (18.4)	1,000	24 (2.3)	0.00000

[a]% of total number of children. [b]Fischer's exact method.

[1]https://doi.org/10.2340/00015555-1989

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

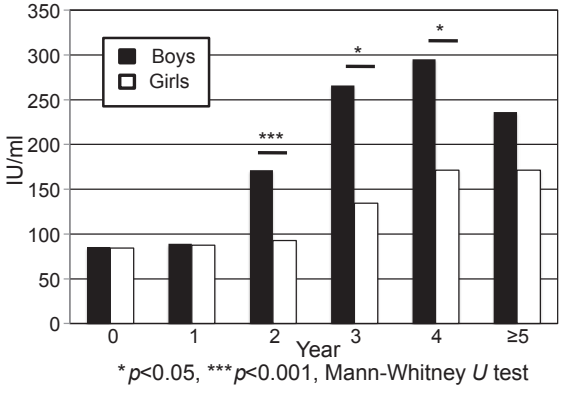
Among the 743 children examined in 2008, blood samples were successfully obtained from 696 children, from whom we received 520 valid answers to the questionnaire. The mean TARC levels of non-allergic children decreased with age, while those of the AD group did not change with age (Fig. 3).

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 reduces the



Age	Boys	Girls
0	52	35
1	391	376
2	443	354
3	316	263
4	208	215
5	97	91

Fig. 1. Total serum IgE levels based on gender and age differences in nursery school children from Ishigaki Island. The data on total IgE levels were obtained from 2,841 blood samples (1,507 boys and 1,334 girls) taken from 2001 to 2009, without individual duplication. *$p < 0.05$ and ***$p < 0.001$ using the Mann-Whitney *U* test.

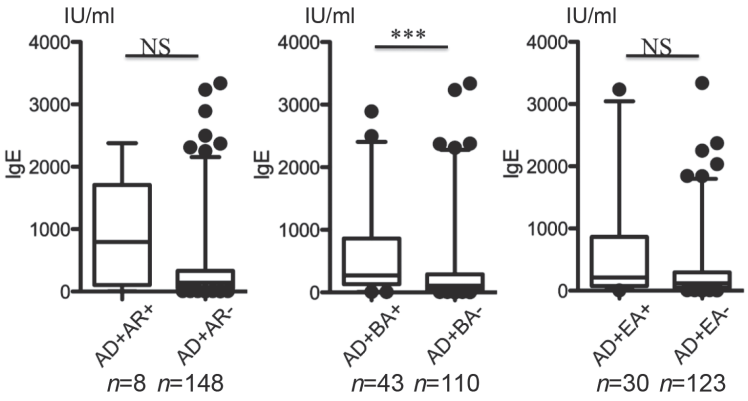


Fig. 2. Total serum IgE levels in nursery school children from Ishigaki Island who have atopic dermatitis (AD) coexistent with other allergic diseases. These data were obtained from questionnaires and blood samples obtained from 2006 to 2008, excluding individual duplication. ***$p < 0.001$ using the Mann-Whitney *U* test. AR: allergic rhinitis; BA: bronchial asthma; EA: egg allergy. NS: non-significant.

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[1]).

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[1]). 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

This work was financially supported by a research grant from the Ministry of Health, Labour, and Welfare, Japan.

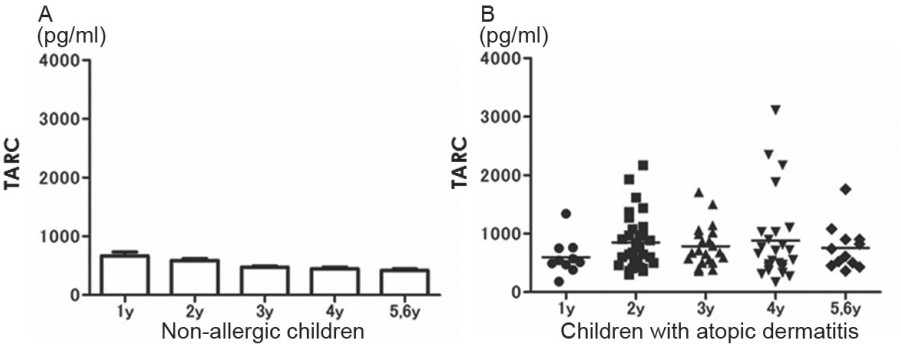


Fig. 3. Changes in serum TARC levels according to the age of nursery school children from Ishigaki Island who have no allergies or have atopic dermatitis. The data were obtained from blood samples taken in 2008.

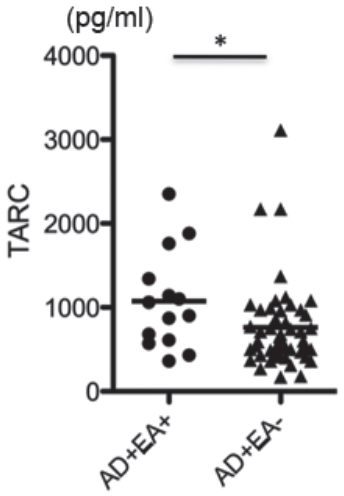


Fig. 4. Mean serum TARC levels of nursery school children with incidental atopic dermatitis (AD) and coexistent incidenatal egg allergy (EA) are significantly higher than those of children without EA. The data were obtained from questionnaires and blood samples in 2008. $*p < 0.05$ by Mann-Whitney *U* test.

The authors declare no conflict of interest.

REFERENCES

1. Williams HC. Is the prevalence of atopic dermatitis increasing? Clin Exp Dermatol 1992; 17: 385–391.
2. Williams H, Robertson C, Stewart A, Aït-Khaled N, Anabwani G, Anderson R, et al. 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.
3. Takeuchi M, Ueda H. Increase of adult atopic dermatitis (AD) in recent Japan. Environ Dermatol 2000; 7: 133–136.
4. Sugiura H, Umemoto N, Deguchi H, Murata Y, Tanaka K, Sawai T, et al. Prevalence of childhood and adolescent atopic dermatitis in a Japanese population: comparison with the disease frequency examined 20 years ago. Acta Derm Venereol 1998; 78: 293–294.
5. Maksimović N, Janković S, Marinković J, Sekulović LK, Zivković Z, Spirić VT. Health-related quality of life in patients with atopic dermatitis. J Dermatol 2012; 39: 42–47.
6. Hamada M, Furusyo N, Urabe K, Morita K, Nakahara T, Kinukawa N, et al. Prevalence of atopic dermatitis and serum IgE values in nursery school children in Ishigaki Island, Okinawa, Japan. J Dermatol 2005; 32: 248–255.
7. Fukiwake N, Furusyo N, Kubo N, Takeoka H, Toyoda K, Morita K, et al. Incidence of atopic dermatitis in nursery school children – a follow-up study from 2001 to 2004, Kyushu University Ishigaki Atopic Dermatitis Study (KIDS). Eur J Dermatol 2006; 16: 416–419.
8. Fukiwake N, Furusyo N, Takeoka H, Toyoda K, Kubo N, Kido M, et al. Association factors for atopic dermatitis in nursery school children in Ishigaki islands – Kyushu University Ishigaki Atopic Dermatitis Study (KIDS). Eur J Dermatol 2008; 18: 571–574.
9. Furusyo N, Takeoka H, Toyoda K, Murata M, Maeda S, Ohnishi H, et al. Thymus and activation regulated chemokines in children with atopic dermatitis: Kyushu University Ishigaki Atopic Dermatitis Study (KIDS). Eur J Dermatol 2007; 17: 397–404.
10. Saeki H, Furue M, Furukawa F, Hide M, Ohtsuki M, Katayama I, et al. Guidelines for management of atopic dermatitis. J Dermatol 2009; 36: 563–577.
11. Yamamoto S. Prevalence and exacerbation factors of atopic dermatitis. Skin Allergy Frontier 2003; 1: 85–90.
12. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. 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.
13. Tan SP, Abdul-Ghaffar S, Weller RB, Brown SB. Protease-antiprotease imbalance may be linked to potential defects in profilaggrin proteolysis in atopic dermatitis. Br J Dermatol 2012; 166: 1137–1140.
14. Sasaki T, Furusyo N, Shiohama A, Takeuchi S, Nakahara T, Uchi H, Hirota T, Tamari M, Shimizu N, Ebihara T, Amagai M, Furue M, Hayashi J, Kudoh J. Filaggrin loss-of-function mutations are not a predisposing factor for atopic dermatitis in an Ishigaki Island under subtropical climate. J Dermatol Sci. 2014; 76: 10–15.
15. Ballardini N, Kull I, Söderhäll C, Lilja G, Wickman M, Wahlgren CF. Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: a report from the BAMSE birth cohort. Br J Dermatol 2013; 168: 588–594.
16. Trzeciak M1, Gleń J, Bandurski T, Sokołowska-Wojdyło M, Wilkowska A, Roszkiewicz J. Relationship between serum levels of interleukin-18, IgE and disease severity in patients with atopic dermatitis. Clin Exp Dermatol 2011; 36: 728–732.
17. Nakazato J, Kishida M, Kuroiwa R, Fujiwara J, Shimoda M, Shinomiya N. Serum levels of Th2 chemokines, CCL17, CCL22, and CCL27, were the important markers of severity in infantile atopic dermatitis. Pediatr Allergy Immunol 2008; 19: 605–613.
18. Leung TF, Ma KC, Hon KL, Lam CW, Wan H, Li CY, et al. Serum concentration of macrophage-derived chemokine may be a useful inflammatory marker for assessing severity of atopic dermatitis in infants and young children. Pediatr Allergy Immunol 2003; 14: 296–301.
19. Hill DJ, Hosking CS, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V, et al. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: An international study. Clin Exp Allergy 2008; 38: 161–168.