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# *Original Articles*

# IgE Food Sensitizations Amongst Children with Atopic Eczema

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**Abstract** ***Background:*** Despite an increasing body of clinical and laboratory evidence suggesting that food hypersensitivity plays a pathogenic role in Atopic Eczema (AE) in a subset of patients, whether IgE food sensitization has any impact on the clinical severity of AE is not clearly established. ***Objective:*** To investigate the association between the severity of eczema and immunoglobulin E mediated food sensitization among atopic eczema children in Hong Kong. ***Study Design:*** A retrospective chart review study of total 77 atopic eczema cases (age 0-14 years) was carried out. The eczema severity scores (three item severity scores TIS), skin prick test results (wheal diameters), and food specific immunoglobulin E levels, clinician diagnosed food allergy were recorded as main outcome measures. Immunoglobulin E mediated food sensitization was diagnosed when the skin prick test resulted in a wheal diameter of greater than 3 mm compared with the negative control and serum food specific immunoglobulin E level greater than 0.35 ku/L. ***Result:*** Overall IgE food sensitization to at least 1 food by either skin prick test or blood test was 81.8%. Eczema severity by TIS was not correlated with the frequency of immunoglobulin E mediated food sensitizations (p-value=0.1346). More than 60% of children in this study developed eczema before 6 months old and this early onset eczema group was highly associated with egg, cow's milk and fish sensitizations (p-value=0.0179, 0.015, and 0.0468 respectively). A positive association was found between the eczema severity and serum total IgE level (p-value=0.002). ***Conclusion:*** IgE food sensitization is very common in this small cohort of Hong Kong children with atopic eczema. Most eczema children with or without clinical history of food reactions have shown positive SPT and CAP-FEIA, or one of the two. Severity of atopic eczema is positively associated with the levels of total IgE. It was not shown that any particular food sensitization was associated with severity of eczema.

**Key words** Atopic eczema; Food allergy; IgE; RAST; Skin prick test

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## Introduction

Atopic eczema (AE) is a chronic inflammatory skin disease commonly affecting the children in industrialised countries.[1] Nowadays 10%-15% of Hong Kong children are suffering from eczema of a wide range of severity. Atopic eczema children usually have sleep disturbance and poor quality of life.[2,3] As atopic eczema is under the category of classical atopic disease, most cases are multi-system allergic diseases.[2,4] Among all associated diseases, food allergy is a common co-morbid condition in eczema children. Early diagnosis of suspected food allergy is important for early intervention and dietary manipulation since no curative therapy has been developed for both AE and food allergy.[5] IgE food sensitization (IgE-FS) can be diagnosed by either skin prick test (SPT) or serum food specific IgE test. IgE food allergy (IgE-FA) requires the presence of a convincing history and sometimes also needs to be confirmed by food challenge test.[6,7] One previous study found Australian infants[8] had not much difference in pattern of food allergy to common food in Australia and Asia, and egg was the most frequent food allergen. Many studies in North America and Australia confirmed the positive association between AE and IgE-FS.[9-12] It has been proposed that the more severe the eczema, the higher is the chance of IgE-FS/FA. Most of the studies adopted SCORAD (SCORing Atopic Dermatitis) or modified SCORAD for assessment of eczema severity score. We aimed to discern that association of frequency of IgE mediated food sensitization and the severity of eczema in eczema children in Hong Kong by using Three-item severity score (TIS). TIS is commonly employed in clinical practice and is proposed to be a reliable global scoring system to evaluate the intensity of "Redness, Odema, and Scratches (excoriations)" on one representative skin lesion.[13] It seems much easier to use comparing to SCORAD, one of the best validated systems, is suited for clinical trials, but is too complicated and time consuming for routine clinical use.

## Method

**Study design, subjects and setting:** Consecutively 77 AE children, between the ages 0-14 years, attending the Allergy & Immunotherapy Clinic of Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, the teaching hospital of the University of Hong Kong, were recruited from January 2007-December 2008. The AE diagnosis was adapted from UK Working Criteria.[4]

The diagnosis requires evidence of itchy skin (or parental report of scratching or rubbing) plus three or more of the following:

- History of involvement of the skin creases (e.g., fronts of elbows, backs of knees, fronts of ankles, and areas around the neck or eyes)
- History of asthma or allergic rhinitis /hay fever (or history of atopic disease in a first-degree relative if the child is under four years of age)
- History of generally dry skin in the past year
- Onset in a child under two years of age (criterion not used if the child is under four years of age)
- Visible flexural dermatitis (including dermatitis affecting the cheeks or forehead and outer aspects of limbs in children under four years of age).

Children who were diagnosed with other immune diseases were basically excluded from this study. The patients were under standard clinical care. All parents or guardians gave verbal consent for blood test and skin prick test. It is our clinic's routine practice to obtain children's verbal assent for skin test and blood test if they are older than 7 years. The retrospective review was approved by Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster in January 2009.

**Main outcome measures:** We applied Three-item severity score (TIS) method to evaluate the intensity of Redness, Oedema, and Scratches (excoriations) on one representative skin lesion.[13] The intensity of redness, oedema and scratch was presented as R-O-S (absent=0, mild=1, moderate=2, severe=3). The maximum score is 9 (mild eczema=<3, moderate eczema=3-6, and severe eczema=>6).[13] The severity score was documented within the 2 months or to the closest date of IgE allergen testing. IgE antibodies to common foods were measured with the CAP system fluorescent enzyme immunoassay (FEIA, Pharmacia, Uppsala, Sweden). IgE-FS was defined when wheal diameter greater than 3 mm compared with the negative control and food specific IgE level greater than 0.35 ku/L.[14] We applied the SPT and serum food specific IgE age specific cut-off values for diagnosis of IgE mediated food allergy (IgE-FA). Age of onset of eczema, serum total IgE levels, peripheral eosinophil count and other relevant histories such as history of adverse food reaction, history of allergic rhinitis, history of anaphylaxis, and family history of atopy, infant feeding history before the age of onset of eczema were also collected to evaluate other possible associations.

**Statistical analysis:** We compared IgE-FS between 2 different severity groups (Mild vs Moderate to Severe) by SPT and serum food specific IgE test in addition to the history of adverse food reaction. The associations between the age of onset of eczema and eczema severity, age of onset of eczema and IgE-FS were investigated by Chi-square test. The pattern of IgE-FS between the groups was compared by Fisher's Exact test. Statistical significance was defined if p-value <0.05. Mann-Whitney test was applied to evaluate the association between serum total IgE and eczema severity and gender difference in total IgE level. The relationship between peripheral eosinophil count and eczema severity was assessed by ANOVA test.

## Results

The comparison of clinical characteristics of subjects by eczema severity was tabulated (Table 1). Comparing the two groups (Mild *vs* Moderate to Severe), there were no differences in age, sex, breast feeding, atopic co-morbidities, family history of atopy, and history of food adverse reactions. Overall**,** the median patient age at allergy testing was 38th month (range=0-144 months) and the mean age of onset of eczema was 9.9 months (range=0.25-48 months). Overall IgE-FS to at least 1 food by either skin prick test or blood test was 81.8%. It was observed that eczema severity was not correlated with the overall frequency of IgE-FS (p-value=0.1346). Comparing the pattern of common food sensitization between the groups (Table 2), milk and shellfish sensitizations were found to be significantly higher in moderate to severe eczema group (p-value, 0.0283 and 0.0437 respectively). Egg, peanut, fish and soy sensitizations were higher in mild eczema group though p-values were not significant. The IgE food allergy is defined by widely accepted international cut-offs of SPT or CAP-FEIA which are age specific.[14] The results were tabulated (Table 3a). The age specific cut offs are often grouped as <2 years old and ≥2 years old. According to SPT cut-off values, only 3 cases had milk allergy, 22 cases had egg allergy, 26 cases had peanut allergy. When we compared IgE-FA by CAP-FEIA cut-off values, egg allergy was significant among all foods (p-value=0.0026). The different criteria to ascertain the IgE FA was also tabulated

**Table 1** Comparison of clinical characteristics of subjects by eczema severity (Three item score TIS)

| | Mild (n=45) | Moderate to severe (n=32) | p-value |
|---|---|---|---|
| **Demographic** | | | |
| Mean age at allergy testing (months) (SD) | 46.7 (41.7) | 54.9 (35.1) | 0.3674 |
| Mean age of onset (months) (SD) | 10.9 (11.7) | 8.6 (11.5) | 0.3947 |
| 0-6 months | 26 (57.8%) | 24 (75%) | 0.1492 |
| 7-12 months | 6 (13.3%) | 2 (6.3%) | 0.4574 |
| >12 months | 12 (26.7%) | 6 (18.8%) | 0.5858 |
| Male sex | 25 (55.6%) | 16 (50%) | 0.6507 |
| Exclusive breast feeding before the onset of eczema | 12 (26.7%) | 9 (28.1%) | 1 |
| Exclusive formula feeding before the onset of eczema | 11 (24.4%) | 10 (31.3%) | 0.606 |
| Mixed feeding before the onset of eczema | 22 (48.9%) | 13 (40.6%) | 0.4962 |
| History of adverse food reaction | 38 (84.4%) | 23 (71.9%) | 0.255 |
| Allergy co-morbidity (allergic rhinitis, asthma) | 19 (42.2%) | 14 (43.8%) | 1 |
| Family history of atopy | 24 (53.3%) | 24 (75%) | 0.0609 |
| **Laboratory** | | | |
| Total IgE >100 IU/ml | 17/24 (71%) | 19/23 (82.6%) | 0.4936 |
| Mean total IgE (SD) | 931.1 (2492.5) | 3433.6 (4635.2) | **0.002*** |
| Mean Eosinophil count (SD) | 0.7 (0.5) | 0.8 (0.5) | 0.3899 |
| IgE-FS by CAP-FEIA – any food | 28 (62.2%) | 24 (75%) | 0.3244 |
| IgE-FS by SPT – any food | 28 (62.2%) | 16 (50%) | 0.3524 |
| IgE-FS by combine SPT/CAPFEIA – any food | 34 (75.6%) | 29 (90.6%) | 0.1346 |

*Mann-Whitney test

(Table 3b). As demonstrated by different methods, the variability could be quite high. It was found that egg (54 out of 77) and peanut allergies (50 out of 77) were very common among this group of atopic eczema. Concerning the age of onset of eczema, more than 60% of cases in this study were early onset. No significant association was found between the age of onset of eczema and eczema severity. The pattern of common food sensitizations was different according to their ages of onset of eczema. Early onset eczema group (<6 m) was highly associated with egg, cow's milk and fish sensitizations (p-value=0.0179, 0.015, and 0.0468 respectively). Regarding the eczema severity, shellfish sensitization was significant in early onset-moderate to severe eczema group (p-value=0.0212). In this study, total 91% of eczema cases had total IgE level higher than normal value 100 IU/ml and the level of serum total IgE was significantly associated with the eczema severity (Mild vs Moderate to Severe = Mean total IgE (SD) 931.1 (2492.5) vs 3433.6 (4635.2); p-value=0.002). Serum total IgE level was higher in male patients but not significant. There was no positive correlation between peripheral eosinophil count and eczema severity. We performed 3 groups (mild, moderate and severe) analysis of Food-Specific-IgE with individual food items among children with different severity of atopic eczema (Figure 1). There were no statistically significant differences among mild, moderate and severe groups. Three group comparison of total IgE level showed a good correlation resembling a 'dose-dependent' manner (Figure 2).

**Table 2** Pattern of IgE food sensitization (IgE-FS) to common foods according to eczema severity

| IgE-FS | Mild (n=45) | Moderate to severe (n=32) | p-value |
|---|---|---|---|
| **IgE-FS by CAP-FEIA** | | | |
| Milk | 10 (22.2%) | 15 (46.9%) | **0.0283** |
| Egg | 20 (44.4%) | 20 (62.5%) | 0.1653 |
| Peanut | 13 (28.9%) | 16 (50%) | 0.0941 |
| Fish | 11 (24.4%) | 8 (25%) | 1 |
| Soy | 4 (8.9%) | 6 (18.8%) | 0.3035 |
| Wheat | 6 (13.3%) | 7 (21.9%) | 0.3665 |
| Any food | 28 (62.2%) | 24 (75%) | 0.3244 |
| **IgE-FS by SPT** | | | |
| Milk | 4 (8.9%) | 8 (25%) | 0.065 |
| Egg | 19 (42.2%) | 15 (46.9%) | 0.8164 |
| Peanut | 24 (53.3) | 10 (31.3%) | 0.0656 |
| Any food | 28 (62.2%) | 16 (50%) | 0.3524 |
| **IgE-FS by SPT/CAP-FEIA** | | | |
| Milk | 14 (31.1%) | 17 (53.1%) | 0.0626 |
| Egg | 28 (62.2%) | 26 (81.3%) | 0.0831 |
| Peanut | 30 (66.7%) | 20 (62.5%) | 0.8097 |
| Fish | 13 (28.9%) | 9 (28.1%) | 1 |
| Soy | 13 (28.9%) | 6 (18.8%) | 0.4228 |
| Wheat | 7 (15.6%) | 7 (21.9%) | 0.555 |
| Shellfish | 3 (6.7%) | 8 (25%) | **0.0437** |
| Any food | 34 (75.6%) | 29 (90.6%) | 0.1346 |

**Table 3a** IgE food allergy (IgE-FA) according to eczema severity

| IgE-FA | Mild (n=45) | Moderate to severe (n=32) | p-value |
|---|---|---|---|
| **IgE-FA by SPT** | | | |
| Cow's milk | 1 (2.2%) | 2 (6.25%) | 0.5669 |
| Egg | 15 (33.3%) | 7 (21.9%) | 0.3151 |
| Peanut | 21 (46.7%) | 5 (15.6%) | **0.0067** |
| **IgE-FA by CAP-FEIA** | | | |
| Cow's milk | 0 (0%) | 3 (9.4%) | 0.0678 |
| Egg | 8 (17.8%) | 8 (25%) | 0.5704 |
| Peanut | 4 (8.9%) | 6 (15.6%) | 0.3035 |
| Fish | 3 (8.9%) | 5 (15.6%) | 0.2654 |
| Soy | 3 (6.7%) | 0 (0%) | 0.2618 |

**Table 3b** Ascertain IgE food allergy (IgE-FA) by different assessments

| Method of assessment | IgE-FA | | | | | |
|---|---|---|---|---|---|---|
| | Milk | Egg | Peanut | Fish | Soy | Wheat |
| History positive, specific IgE positive (SPT>=3 mm or CAP-FEIA>=0.35 ku/L) | 31 | 54 | 50 | 22 | 19 | 14 |
| No history, CAP-FEIA>cut-off values | 3 | 16 | 10 | 8 | 3 | 0 |
| History positive, CAP-FEIA>cut-off values | 3 | 16 | 9 | 8 | 3 | 0 |
| History positive, SPT>cut-off values | 3 | 22 | 26 | N/A | N/A | N/A |

N/A=NO available cut-off value

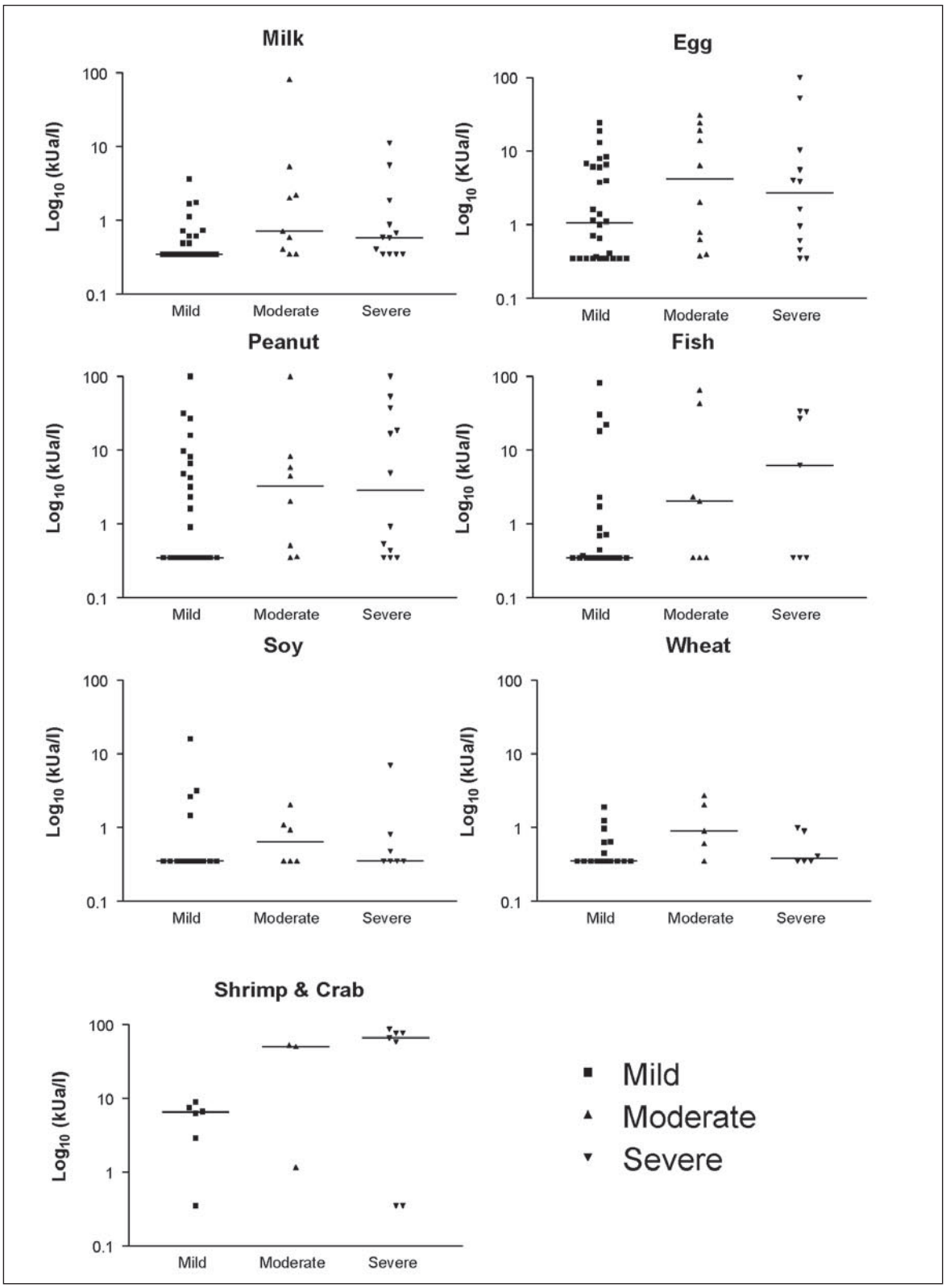


**Figure 1** Scatter plots of Food-Specific-IgE with individual food items among children with different severity of atopic eczema. The horizontal bar represents the median food specific IgE level of the respective severity group. There are no statistically significant differences among mild, moderate and severe groups.

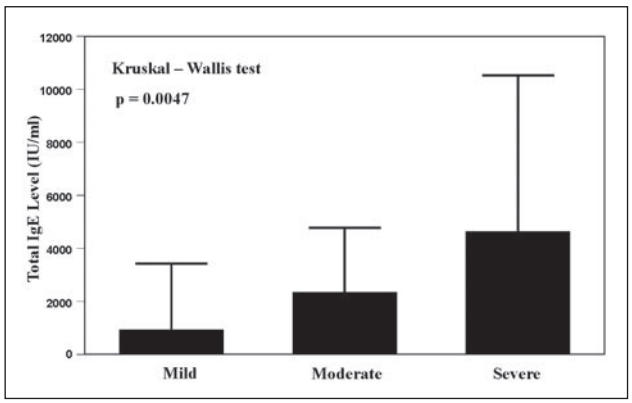


**Figure 2** Total IgE level and eczema severity.

## Discussion

Some well-designed studies have demonstrated the strong association between AE and IgE-FS.[9-11] In this study, more than 80% of eczema children had IgE-FS to at least one food item. This was similar to what other studies had shown. A large, cohort international study,[10] suggested that the "earlier the age of onset, the greater the frequency of associated high levels of IgE-FS". We could see such a trend but it did not reach statistical significance in our study. Comparing their suggestion "the earlier the age of onset, the greater the severity of eczema", the percentages of moderate to severe cases were apparently higher and percentage of mild cases was apparently lower in early onset eczema group in our study. Again our finding lent support to this proposition but not reaching statistical significance. One study recently carried out in Hong Kong compared the common IgE-FS and aeroallergens in infantile AE and older children with AE[15] and the authors concluded that milk sensitization was less prevalent than egg white among eczema children. Our finding corroborated their findings as egg and peanut sensitizations were significantly higher in our eczema children compared among other common foods (p-value=<0.0001). Most studies, including this study, revealed that egg allergy was the most common food allergy in eczema children. It was obvious that prevalence of egg allergy has been increasing among eczema children all over the world regardless of different traditional foods and life styles. We have a very high food sensitization among our eczema children but the clinical relevance to diagnose food allergy was not that straightforward. Judicious use of allergen testing in conjunction with clinical history correlation and appropriate food challenge is the way to discern the role of food hypersensitivity in individual patients.

One interesting finding in our study was that serum total IgE levels were significantly higher in severe eczema group which was identical to the one literature finding.[16] Most patients with AE have peripheral eosinophilia and increased serum IgE levels. Nearly 80% of children with AE develop allergic rhinitis or asthma. Because serum IgE level is strongly associated with the prevalence of asthma, it suggests that allergen sensitization through skin predisposes the patient to respiratory disease because of its effects on the systemic allergic response. Total serum IgE though correlates well with AE severity but it overlaps with other atopy and non atopic diseases and is thus considered not specific enough to offer advice on allergen avoidance and to guide intervention. Also because it often correlates quite well with validated clinical scores and hence it has no extra gain for practical purposes, though it may bear prognostic implication.

Total IgE is a crude measurement and a summation of many specific IgE subsets and also some non specific IgE with low affinity to a wide range of pan-allergens. Studies have shown that there are specific IgE subsets other than foods and dust mites such as IgE against auto-allergen,[17] IgE against fungal colonization,[18] IgE against super-antigen to staphylococcus[19] which might be more useful than a total measurement of IgE as AE severity marker and as guidance for treatment. However, a wider clinical application of these promising research tools is very much hampered by the limited availability, relative high cost and perhaps some difficulty in clinical validation.

Those with exceptional high IgE in association with bad atopic dermatitis are likely to have a genetic susceptibility. A novel *IL13* coding region variant was implicated in the pathogenesis of AE and high total serum IgE level in a German study of white subjects.[20] Such implication in Chinese has not yet been studied.

## Limitation

Due to the retrospective nature of the study, we encountered some limitations. First, there may be referral bias as the sample was recruited from the children referred for assessment of food allergy as a precipitating factor for flare-up of their eczema. Hence, the generalisation of result may not be appropriate to community setting. However, as mild cases constituted more than 50% which might be 'over-represented', it would probably argue for applying our findings to community settings where most cases are mild. As a matter of fact, more severe cases were over referred to

the dermatology clinic and we are currently evaluating the IgE sensitization in a group of eczema patients cared by dermatologist. Second, due to the small sample size, we were unable to discern if there were any relationships between mean age at testing, IgE food sensitization and clinical severity. Third, TIS scoring requests for an assessment of a representative lesion which may over simplify the clinical picture resulting in errors and inconsistency at occasions. Different scoring systems have been developed to determine the severity of atopic dermatitis. The SCORAD, one of the best validated systems, is suited for clinical trials, but is too complicated and time consuming for routine clinical use. In a prospective study in 126 children with mild to severe atopic dermatitis, both the TIS score and the SCORAD were assessed by trained investigators. Inter-observer agreement was investigated in 20 children by comparing the independently performed scores of three investigators. A positive correlation was found between the TIS score and the SCORAD. The item which correlated best with the SCORAD was excoriation followed by oedema/papulations. Inter-observer agreement was "excellent" for SCORAD and "fair" for TIS score. The authors concluded that the TIS score was a rough, but reliable and simple system for scoring atopic dermatitis. It is particularly suitable in general practice, for routine clinical use and for screening purposes in clinical trials. For research purposes, the objective SCORAD offers a more detailed and comprehensive assessment.[21] Hence, to compare TIS and SCORAD about the association of IgE-FS in a prospective cohort will be pertinent.

According to Leung and his colleagues' questionnaire based study[22] of parent-reported adverse food reaction in Hong Kong pre-schoolers (2-7 years), the prevalence rate of parent-reported AFR was 8.1% and more than half of them had doctor-confirmed diagnosis. These were comparable to the Caucasian data. The six leading foods were shellfish, egg, peanut, beef , cow's milk, and tree nuts. A scientifically robust global prevalence study, the EuroPrevall-INCO project has been developed to evaluate the prevalence of food allergies in China, India and Russia using the standardised protocol adapted from Europe.[23] The study is ongoing and Hong Kong is one of the investigational sites. Such result is eagerly awaited by paediatrcians, allergists and other professionals alike. Hon et al reported that IgE sensitization to common food allergens was common in Hong Kong infants with or without eczema. Majority of young infants were not sensitized to milk, and develop eczema before they show atopy to the milk or soy allergens.[24] This corroborated to the growing evidence that food allergy is perhaps secondary to barrier breakdown in eczema infants. In an attempt to evaluate the correlations between conventional marker (IgE, eosinophils) versus novel markers (cutaneous T-cell-attracting cytokine (CTACK), thymus and activation-regulated chemokine (TARC) and clinical severity and patient symptomatology, Hon et al demonstrated that these markers may have a differential role in predicting clinical severity by SCORAD[25] but the exact clinical application remains to be defined.

The taking or avoidance of food was often based on belief in Hong Kong. Patients with moderate-to-severe AE were more likely to have consumed 'bird's nest' soup and traditional Chinese medicine.[26] Management is perceivably suboptimal if children with food allergy and severe disease continue to consume the culprit food. Conversely, avoidance of common food in children without food allergy could result in food faddism or malnutrition. One interesting observation is that despite some parents thought beef is an important food allergen related to exacerbation of eczema, Hon et al found only 13% of 114 children with eczema had a positive SPT for beef. They alluded that SPT information may be useful in reassuring parents about the unlikelihood of a severe and immediate reaction to beef.[27]

Despite the focus of parents is often targeted on food avoidance issues, we cannot overlook the importance of aeroallergen such as house dust mite and furry pets. Hon et al showed that such dust mite sensitization was associated with eczema severity. However, there was no association between eczema severity and higher strengths of SPT response.[28]

Some of the infants had positive sensitization to peanut and shellfish. Indeed very few of them would consume such food at this young age. Hypersensitiviy in the very young children raises questions about how sensitization can occur. Using peanut as an example, peanut products are very difficult to eliminate from the diet because of inadequate labeling of food products and ubiquity of such food in diet. Cutaneous contact via eczematous skin resulting in IgE sensitization is biologically plausible and has been proven by animal studies. Other routes were likely from pregnancy and lactation. Evidence from aborted fetal samples showed that from the second trimester onwards fetuses are capable of producing an allergic reaction. Some research has shown that antigens from the mother could cross the placenta, whereas other work suggested fetuses could swallow IgE from the amniotic fluid, causing sensitization.[29] A South African study[30] showed that mothers who consumed peanuts more than once a week during pregnancy were more likely

to give birth to a peanut allergy child than mothers who consumed peanuts less than once a week.

Vadas et al had shown from laboratory data that peanut protein passed from the maternal diet via the bloodstream into breast milk.[31] The two major peanut allergens associated with anaphylaxis were detected in breast milk within one to three hours after ingestion in about half of the volunteers. These data lent support to the notion that some infants may become sensitized by exposure to peanut protein through breastfeeding.[26,32]

In conclusion, IgE-Food Sensitization is very common in this small cohort of Hong Kong children with atopic eczema but no apparent relationship of the eczema severity (by TIS) and frequency of IgE-FS or IgE-FA. Egg and peanut were the most common food allergies suffering in AE children in Hong Kong. Early onset AE (<6 months) had significant higher risk of egg, milk, and fish sensitizations. Most eczema children with or without clinical history of food reactions have shown positive SPT and CAP-FEIA, or one of the two. Severity of atopic eczema is positively associated with the serum levels of total IgE. It was not shown that any particular food sensitization was associated with severity of eczema.

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## *Erratum*

The original article "Paediatric Narcolepsy: A Rare and Easily Forgotten Diagnosis" written by Dr. Yau MM et al. and published in the April 2011 issue of the Hong Kong Journal of Paediatrics (HK J Paediatr (new series) 2011: 16:131-138) has been inadvertently placed under the category of case report. It should be classified under the original article section.