ORIGINAL ARTICLE

Usefulness of the Skin Index in Predicting the Outcome of Oral Challenges in Children

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Abstract

Background: The diagnostic accuracy of the skin prick test (SPT) for food allergies remains to be fully accepted and substantial individual differences in the prevalence of skin test reactivity have been reported.
Objective: The aim of this study was to assess the diagnostic value of absolute wheal size and skin index (SI; ratio of food allergen-induced wheal to histamine-induced wheal) according to the outcome of controlled oral food challenges.
Methods: Eighty-seven controlled oral challenges were performed with cow's milk, hen eggs, wheat, buckwheat, peanuts, seafood, and/or fruit in 51 children (median age, 35 months). The wheal diameters in SPT, the SI, and the serum specific immunoglobulin (Ig) E concentrations were determined.
Results: Thirty-three oral challenges were assessed as being positive. SI and wheal diameter in SPT were both significantly different according to the outcome of food challenge ($P<.001$ and $P = .03$, respectively); the greatest difference was found in the case of SI. Serum specific IgE concentration did not differ significantly according to the outcome of food challenge.
Conclusion: SI may be helpful for predicting a positive outcome of food challenge.

Key words: Skin prick test. Food allergy. Oral food challenge.

Resumen

Antecedentes: La precisión diagnóstica de las pruebas cutáneas para las alergias alimentarias sigue sin aceptarse por completo. Existen diferencias individuales substanciales en la prevalencia de la reactividad a las pruebas cutáneas.
Objetivo: El objetivo del estudio fue evaluar el valor diagnóstico del índice cutáneo y del tamaño absoluto de las ronchas (proporción de roncha provocada por el alérgeno alimentario frente a roncha provocada por histamina) de acuerdo con el resultado de provocaciones controladas con alimentos por vía oral.
Métodos: Se realizaron 87 provocaciones orales en 51 niños (mediana de edad: 35 meses) con leche de vaca, huevos de gallina, trigo sarraceno, cacahuetes, marisco o fruta. Se determinaron los diámetros de roncha en las pruebas cutáneas, el índice cutáneo y las concentraciones séricas de inmunoglobulina (Ig) E específica.
Resultados: Treinta y tres de las provocaciones orales fueron positivas. El índice cutáneo y el diámetro de roncha en la prueba cutánea fueron ambos significativamente distintos según el resultado de la provocación con alimentos ($P<0{,}001$ y $P = 0{,}03$, respectivamente); la mayor diferencia se apreció en el caso del índice cutáneo. La concentración sérica de IgE específica no difirió significativamente según el resultado de la provocación con alimentos.
Conclusión: El índice cutáneo puede ayudar a predecir un resultado positivo de la provocación con alimentos.

Palabras clave: Prueba cutánea. Alergia alimentaria. Provocación oral con alimentos.

Introduction

A combination of the increasing prevalence of food allergies in children and greater public awareness has led to an increase in the demand for assessment of suspected food allergies. While double-blind, placebo-controlled food challenges still represent the gold standard for the diagnosis of food allergies, they are time consuming, expensive, and troublesome for the patient and involve the risk of severe systemic reactions [1]. In recent years, efforts have been made to find diagnostic tests for predicting the outcome of oral food challenge. Skin prick test (SPT) [2-4], atopy patch test [5], and analysis of food-specific serum immunoglobulin (Ig) E [6,7] have been reported to be useful tools for the diagnostic workup of food allergies. However, they still do not render oral food challenges unnecessary in most cases [8].

As SPT is easy to perform, rapid, and inexpensive, it appears to be a valuable first-line procedure for the evaluation of food allergies. However, despite its high sensitivity, its specificity is rather low [3]. Therefore, by simply considering the reaction as positive or negative, SPT alone may not provide sufficient proof of a clinically relevant food allergy. In addition to measurement of absolute wheal sizes in SPT, we can calculate the skin index (SI), namely the ratio of a food allergen-induced wheal to a histamine control reaction, and this approach may reveal differences in individual dermal reactivity [9]. The aim of this study was to retrospectively assess the diagnostic value of absolute wheal size and SI according to the outcome of controlled oral food challenges.

Materials and Methods

Patients

A retrospective study was performed involving 51 children (median age, 35 months; range, 6-91 months), of which 33 were boys, seen in 2004 in the Department of Child Development, Kumamoto University Hospital, Kumamoto, Japan, with suspected allergies to cow's milk and dairy products, hen eggs, cereals, peanuts, seafood, and/or fruit (Table 1). The following children underwent food challenges: (i) those who exhibited a previous adverse reaction to food, namely urticaria (n = 10), angioedema (n = 5), wheezing (n = 3), gastrointestinal symptoms (n = 7), anaphylactic shock (n = 2), skin symptoms plus wheezing (n = 9), and skin symptoms plus wheezing and gastrointestinal symptoms (n = 2); and (ii) those with a positive SPT response who had not knowingly eaten the food before (n = 13). All patients had avoided suspect food before the tests. Eleven children (22%) had atopic dermatitis, according to the criteria of Hanifin and Rajka [10], and 7 (14%) had asthma. SPT was performed and blood samples were taken on the day of initial assessment. All data used in the retrospective analysis were obtained from hospital records.

Table 1. Patient Characteristics*

Food Allergy	No. of Patients	Age, Months
Hen egg	31 (17/14)	34 (12 – 91)
Cow's milk	21 (14/7)	35 (7 – 85)
Wheat	7 (7/0)	22 (6 – 85)
Buckwheat	2 (2/0)	65 (47 – 82)
Peanuts	4 (2/2)	55 (13 – 85)
Fish	13 (8/5)	28 (16 – 82)
Crustaceans	4 (2/2)	40 (22 – 90)
Fruit	5 (5/0)	55 (23 – 82)

*Data are shown as number of patients (male/female) and mean age (range).

Skin Prick Test and Specific IgE Analysis

Commercial food extracts at a dilution of 1:20 (w/v) in 50% glycerin were obtained from Torii-Yakuhin Co (Tokyo, Japan). One drop of each glycerinated food extract was applied to a patient's forearm. SPT was performed with plastic twin-tip needles (Duotip-Test, Lincoln Diagnostics, Illinois, USA), and the diameters of the wheals were determined after 20 minutes. Histamine diphosphate (10 mg/mL; Nacalai Tesque, Kyoto, Japan) and saline solution were used as positive and negative controls, respectively. All tests with a wheal diameter below 3 mm elicited by histamine or with a wheal of more than 2 mm elicited by the saline solution were excluded, and the result for each allergen was defined as positive if the mean wheal diameter was 3 mm or greater [11]. The SI was calculated as the ratio of allergen-induced wheal diameter to histamine-induced wheal diameter. Patient sera were analyzed for specific IgE antibody titers by fluorescence enzyme immunoassay using the Pharmacia CAP system (Pharmacia Diagnostics, Uppsala, Sweden). Children with specific IgE levels above the detection limit of the CAP system (0.35 kU/L) were considered sensitized.

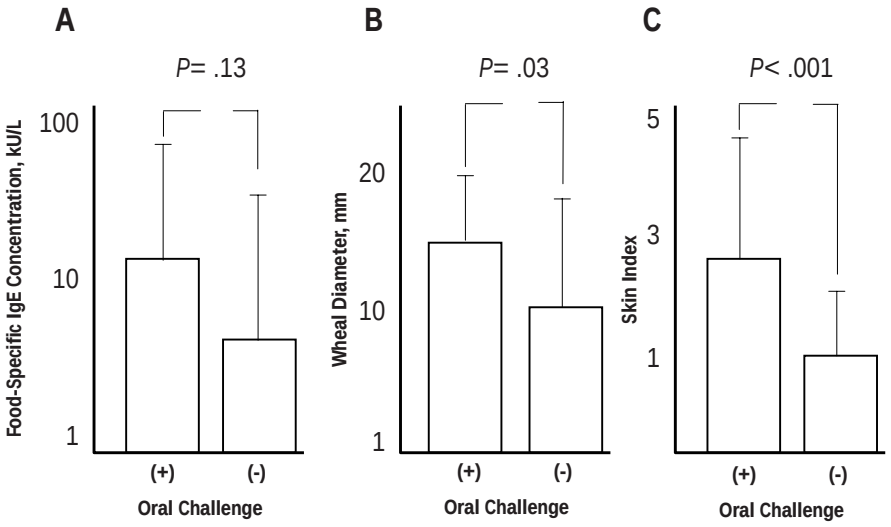
Oral Food Challenge

Since there are no internationally accepted protocols for oral food challenge, protocols were developed based on the currently available literature [12]. Briefly, in most patients, successive doses of food were given up to a total of 1 g equivalent dried food per kg of body weight, except in cases where the patient's chart clearly indicated otherwise. The required amount of food was calculated as follows: 1 g of dried product per kg body weight in 8 mL of cow's milk, containing 87.5% water. The provocation was stopped if clinical symptoms were observed or the highest dose was reached. At the end of a negative challenge, the child was expected to be able to consume a normal amount of the food. If the child refused the food at this stage, the parents were asked to give a normal portion of this food to the child at home.

Statistics

The results obtained for SPT wheal diameters, SI, and serum specific IgE titers were compared in patients with positive and negative results for oral challenge using the Mann-Whitney *U* test. Comparisons were considered to be statistically significant when *P* was less than .05.

Two-by-two tables were used to calculate sensitivity, specificity, positive predictive value, and negative predictive



Results of skin prick testing and food-specific immunoglobulin (Ig) E titer in patients with positive and negative response to oral food challenge.
A) Log_{10} serum specific IgE concentrations. B) Absolute wheal diameter in the skin prick test. C) Skin index, defined as the ratio of food-allergen induced wheal to histamine-induced wheal. Bars indicate means and whiskers SD. Comparisons between patients with positive and negative responses to oral challenge were made by Mann-Whitney *U* test.

value. Test sensitivity was defined as the proportion of true positives detected and specificity as the proportion of true negatives detected. The positive predictive value was defined as the proportion of symptomatic individuals among positive tests, and the negative predictive value was defined as the proportion of nonsymptomatic individuals among negative tests.

Ethical Approval

The study was approved by the Ethics Committee of the Kumamoto Society for Pediatric Allergies. Informed consent to inclusion in the study was obtained from the parents of all of the children.

Results

A total of 87 controlled oral challenges with hen eggs, cow's milk, cereals, peanuts, seafood, and/or fruit performed in 51 children were analyzed. Eighteen of the 31 (58%) hen-egg challenges, 9 of the 21 (43%) cow's milk challenges, 3 of the 7 (43%) wheat challenges, 1 of the 2 (50%) buckwheat challenges, 2 of the 4 (50%) peanut challenges, none of the 13 (0%) fish challenges, none of the 4 (0%) crustacean challenges, and none of the 5 (0%) fruit challenges were assessed as being positive. Of the 33 positive challenges, 30 (91%) were immediate-type clinical reactions (eg, urticaria, cough, wheezing, gastrointestinal reactions, or hypotension) and 3 (9%) were late-phase reactions involving a skin rash 5 to 9 hours after the challenges with hen eggs or cow's milk.

The wheal diameters ranged from 2 to 25 mm (median, 11.9 mm) for the food extracts and from 3 to 27 mm (median, 7.9 mm) for histamine. The SI ranged from 0.2 to 8.3 (median, 2.1). The food-specific serum IgE titers ranged from less than 0.34 to 103.6 kU/L (geometric mean, 8.1 kU/L). As shown in the figure, significant differences were observed between patients with a positive food challenge and those in whom the results of food challenge were negative in terms of SI and wheal diameter ($P<.001$ and $P = .03$, respectively), whereas no statistically significant difference was obtained between those 2 groups in terms of serum specific IgE titer ($P = .13$). The numbers of patients with true positive and true negative reactions in the SPT and in the serum specific IgE determinations are summarized in Table 2. The results for sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 11%, 41%, and 100%, respectively, for SPT, and 91%, 15%, 40%, and 73%, respectively, for the IgE determinations.

Discussion

The results of this study confirmed that wheal diameters in SPT are significantly different in patients with positive oral food challenge compared with those in whom the results of food challenge are negative [2-6], while serum specific IgE titer does not differ significantly according to the outcome of food challenge. SPT measures the release of histamine, other preformed

Table 2. Numbers of Clinically Reactive or Tolerant Patients With Positive and Negative Results in Skin Prick Test or Analysis of Serum Specific IgE Titer*

		Oral Challenge	
		Positive	Negative
SPT	Positive	33	48
	Negative	0	6
IgE	Positive	30	46
	Negative	3	8

*Data are shown as number of patients. SPT indicates skin prick test; IgE, immunoglobulin E. Positive results in SPT were defined as a mean wheal diameter of 3 mm or greater; positive results for IgE determination were defined as levels above the detection limit of the immunoassay (0.35 kU/L).

mediators, leukotrienes, and prostaglandins produced by mast cells following IgE/allergen interactions at the cell surface. Thus, our study supports the possibility that tissue-fixed IgE antibodies are of greater clinical value for the diagnosis of IgE food allergies than circulating IgE antibody levels.

Various studies have shown that both the sensitivity and specificity of SPT are enhanced by the use of fresh food compared with available commercial extracts [4,13]. However, the use of unprocessed fresh food poses some problems. Firstly, it is difficult to standardize the procedure for prick-to-prick testing with wheat, buckwheat, and peanuts. Secondly, most fruit and vegetables have different varieties and also exhibit seasonal variation. Furthermore, it is necessary to establish the optimal dilution of liquid allergens, such as milk, in order to compare results. As a result of these problems associated with the use of fresh foods, food extracts were used in the patients described here.

Our data demonstrate that the SI is superior to the use of wheal diameters alone for predicting a positive outcome of food challenge based on the results of SPT. Histamine acts directly on skin tissue components, causing vasodilation, increased blood flow, and edema. Thus, it measures the reactivity of the skin [9]. In addition to assessing the absolute wheal diameter in SPT, assessment of SI may reveal differences in individual dermal reactivity.

Although Hill et al [14] proposed that patients with a wheal diameter caused by cow's milk twice the size of that induced by histamine (corresponding to an SI of 2.0) should be regarded as having a food allergy, Verstege et al [4] reported that the SI does not provide any additional information for the daily routine diagnostic workup for cow's milk, hen eggs, or soybeans. The reasons for this discrepancy are not known. One hypothesis is that it is due to the different characters of different foods in terms of diagnostic effectiveness. Consistent with this possibility, a higher proportion of non-IgE-mediated clinical reactions are observed upon challenge with plant proteins [15]. Regarding soybeans, a poor correlation has been reported between the outcome of oral challenge and SPT results [2] or serum specific IgE concentrations [6,7]. Therefore, SPT and serum specific IgE determination for soybean allergy are not performed in our clinic and patients with soy allergy were excluded from the present study.

As an alternative to the use of fresh food, commercially prepared food extracts for use in SPT and CAP occasionally lack the proteins responsible for IgE-mediated sensitivity [4]. For instance, the commercially prepared wheat-flour extract for use with these tests does not contain the water/salt-insoluble gluten fraction that is responsible for the reaction in patients with immediate allergy to ingested wheat [16].

In conclusion, SI showed a better correlation with the outcome of oral food challenge than wheal diameters alone, indicating that oral food challenges may not be necessary in some cases. However, data may need to be obtained for each food separately if food extracts cannot be standardized.

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