Prediction of food allergens sensitization based on history taking technique in young children

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To the Editor

Allergic disease diagnosis begins with a clinical history and physical examination to identify allergic symptoms associated with a relevant allergen.[1] Immunoglobulin E (IgE) antibody sensitization is then confirmed with in vivo skin tests or in vitro blood test. If there is a mismatch between history and these primary sensitization diagnostic tests, then a provocation test may be required. During oral food challenges (OFC), test administrators must be specially trained in acute severe allergic reaction management and OFCs should only be performed with immediate access to intensive care units.[2] Therefore, evaluating specific IgE (sIgE) sensitization are often used to help predict the outcome of the OFC before referring to a well-equipped tertiary hospital.

Skin prick tests are not the preferred diagnostic tool if physicians are not well-trained allergists and in many countries, and typically, the number of antigens that can be evaluated at one time using serologic tests is limited. These limitations lead physicians to prefer to perform the multiple-antigen simultaneous tests for food allergy (FA) diagnosis, the results of which are semi-quantitative and often limited in predicting OFC outcome.[3] The purpose of this study was to analyze the possibility of sIgE antibody detection using troops from self-reported food allergic symptoms.

From May 2011 to December 2013, medical records of 377 patients (3 years old or younger) who visited the Department of Pediatrics at Ajou University Hospital were collected for egg white-, cow's milk-, walnut-, and soybean-sIgE sensitization (sIgE [?] 0.35 kU/L, UniCAP, ThermoFisher Scientific, USA). Five components of patients' clinical history were collected: 1) way of exposure: direct (ingestion) or indirect (skin, inhalation); 2) type of exposure: isolated or mixed; 3) onset time: [?]2 hours or >2 hours; 4) symptom characteristics: anaphylaxis, urticaria, itchiness, vomiting, or diarrhea; and 5) consistency: negative past history or positive past history with consistency or inconsistency. Each clinical history was classified into class 1: direct-isolated intake resulting in anaphylaxis or hives without inconsistency; class 2a: class 1 with inconsistency, class 2b: indirect-mixed intake resulting in anaphylaxis or hives regardless of consistency, or class 2c: direct/indirect-isolated/mixed intake resulting in itch without hives, vomiting, or diarrhea without inconsistency; or class 3: class 2c with inconsistency or asymptomatic to direct, isolated exposure. All class 1 cases that were not of isolated ingestion were considered vague and were reclassified as class 2. An exception was made for anaphylaxis due to skin contact, which was still regarded as class 1. If the symptom onset time was recorded as "next day," these classes were also reclassified by adding 1 (Table 1). Receiver operating characteristic curves were analyzed using SPSS version 22.0 (SPSS Inc., Chicago IL). The study was approved by the Institutional Review Board of Ajou University Medical Center (MED-KSP-12-381).

In class 1 cases, the sensitization rate (i.e., sIgE positive) was the highest in walnuts (9 of 10; 90.0%), followed by hen's egg white (49 of 55; 89.1 %) and cow's milk (71 of 81; 87.7%). However, soybean-sIgE sensitization

was only found in 5 of 8 cases (Table 2). Meanwhile, in class 2 cases, sIgE positivity was found in only 2 of 8 cases for soybean (25%) and 10 of 33 cases for cow's milk (30.3%). However, within class 2 cases, sIgE-positivity was also high for egg white (17 of 22 cases; 77.3%) and walnut (2 of 3 cases; 66.7%). Egg white-sIgE demonstrated an area under the curve (AUC) of 0.717 and a positive predictive value of 89.1% in class 1 cases. When class 2 cases were included in this analysis in addition to class 1 cases, the AUC of egg white-sIgE positivity increased to 0.750, the negative predictive value increased to 68.6% compared with 47.5% for class 1 cases only, and the accuracy increased from 67.2% for class 1 cases only to 77.6% for class 1 and 2 cases. However, for cow's milk- and walnut-sIgE sensitization rate, class 1 cases were the most predictable (AUC of 0.790 and 0.755, respectively), with an accuracy rate of 78.0% and 76.5%, respectively. Soybean-sIgE sensitization rate had a lower AUC of 0.662 in class 1 cases than other allergens (Table 3).

FAs can be highly anticipated if anaphylaxis or objective symptoms are repeated more than once within a few hours after ingestion of a specific antigen.[4] Accordingly, class 1 cases were limited to patients who experienced an immediate onset of objective symptoms (anaphylaxis or hives) after isolated ingestion. This study included patients aged < 3 years who often refused to perform an OFC using unfamiliar foods; hence, this study is limited as an OFC was not often performed. Therefore, the medical history technique described in this study cannot be deemed a definitive method for confirming FA. In fact, in class 3 cases, including asymptomatic or subjective manifestations to allergens, approximately 20–40% were sIgE positive and highly likely to tolerate the specific allergen and therefore would not be deemed to have an FA (sIgE positive: egg white, 38.5%; milk, 29.4%; walnut, 25.0%; and soybean, 33.3%). While it appears that many patients must confirm FA through OFC, even if there is sIgE sensitization, this study provides information for primary physicians who may be limited in implementing OFC. The rate of sIgE sensitization in class 1 cases was high (87.7–90.0% depending on antigen), supporting the detailed collection of important elements of the history taking pertaining to allergens. This study suggests that a clinical history of allergen exposure and characteristics of reactions can help determine whether sIgE sensitization and further OFC testing are required.

Egg white, cow's milk, and tree nuts are known as highly likely to be OFC positive, especially if patients have a history of adverse reactions within 5 minutes of direct exposure.[5] In infants and young children who are allergic to foods, it is rare that they experience respiratory or gastrointestinal symptoms alone and this study continues to support this outcome. When collecting medical history from patients for a suggested FA, physicians must record all symptoms that occur sequentially, including the type of intake, symptom development and characteristics, and previous allergic symptoms after ingestion.

This study demonstrated differences in sIgE sensitization according to the type of food antigen type, and it would be beneficial to add additional history-taking techniques based on these results. For instance, the accuracy of the egg white-sIgE sensitization testing increased when interpreting both class 1 and class 2 cases based on patient history, as it included objective cases of symptoms caused by both direct and indirect exposures. However, the accuracy decreased in the milk-sIgE sensitization testing of class 2 cases. It is thought that this may be due to young patients' subjective symptoms, such as gastrointestinal symptoms alone. As walnuts were frequently consumed in a mixed form rather than isolated, there was a possibility of an increase in accuracy for the walnut-sIgE testing of both class 1 and class 2 cases.

Prior to FA diagnosis, a detailed medical history could screen for potential allergens to be checked for IgE sensitization; however, it does depend on the type of allergen. The sIgE sensitization of egg white, cow's milk, and walnuts are easy to predict by history alone but methods for increasing the predictability of each allergen are slightly different.

Signature

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Author contributions

Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data: SL and JL; Drafting the article or revising it critically for important intellectual content: KJ and JL; Final approval of the version to be published: SL.

Conflict of interest

The authors have no conflict of interest in relation to this work.

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Tables

Table 1. Classification according to patients' clinical history

		Past history and exposure patterns	Past history and exposure patterns	Past h
Onset time	Symptom Characteristics	Consistency (+) or past history (-) Isolated Direct Classification	Consistency (+) or past history (-) Isolated Indirect Classification	Consis Mixed Classif
2 hours*	Anaphylaxis	1	2+	2
	Urticaria (hives)	1	2	2
	Itchy	2	2	2
	Vomit	2	2	2
	Diarrhea	2	2	2
>2 hours	Negative	3	3	3

* Class 1 cases where symptom onset time was recorded as "next day," were reclassified as class 2.

+ All cases that were not direct-isolated intake were considered to be vague. In such cases, class 1 were reclassified as class 2, except were anaphylaxis occurred due to skin exposure.

Table 2. Patient classification and IgE sensitization rate of food allergens in young children

	Class 1	Class 2	Class 3
EW-sIgE [?] 0.35 kU/L*	49/55 (89.1%)	17/22 (77.3%)	15/39 (38.5%)
CM-sIgE [?] 0.35 kU/L	71/81 (87.7%)	10/33 (30.3%)	20/68 (29.4%)
WN-sIgE [?] 0.35 kU/L	9/10 (90.0%)	2/3 (66.7%)	1/4 (25.0%)

	Class 1	Class 2	Class 3
Soybean-sIgE [?] 0.35 kU/L	5/8 (62.5%)	2/8 (25.%)	2/6 (33.3%)

EW, egg white; CM, cow's milk; WN, walnut

* ImmunoCAP (Phadia AB, Uppsala, Sweden)

Table 3. Association between patient classification and predicted IgE sensitization of food allergens in young children

Specific IgE [?] 0.35 kU/L to	Egg white	Egg white	Cow's milk	Cow's milk	Walnut	Walnut	Soybean	Soybean
Class	1	1 and 2	1	1 and 2	1	1 and 2	1	1 and 2
AUC	0.717	0.750	0.790	0.697	0.775	0.758	0.662	0.543
Sensitivity	60.5% (<0.001)	81.5% (<0.001)	70.3% (<0.001)	80.2% (<0.001)	75.0% (0.082)	91.7% (0.102)	55.6% (0.205)	77.8% (0.738)
Specificity	82.9% (<0.001)	68.6% (<0.001)	87.7% (<0.001)	59.3% (<0.001)	80.0% (0.082)	60.0% (0.102)	76.9% (0.205)	30.8% (0.738)
PPV	89.1% (<0.001)	85.7% (<0.001)	87.7% (<0.001)	71.1% (<0.001)	90.0% (0.036)	84.6% (0.022)	62.5% (0.119)	43.8% (0.658)
NPV	47.5% (<0.001)	68.6% (<0.001)	70.3% (<0.001)	70.6% (<0.001)	57.1% (0.036)	75.0% (0.022)	71.4% (0.119)	66.7% (0.658)
Accuracy	67.2%	77.6%	78.0%	70.9%	76.5%	82.4%	68.2%	50%

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value