Follow-up of patients with uncertain symptoms during an oral food challenge is useful for diagnosis

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Abstract

Background: Uncertain symptoms often emerge during an oral food challenge (OFC), and Open-OFCs with those uncertain mild symptoms are ordinarily regarded as positive. Double-blind placebo-controlled food challenges should be conducted to determine these associations. Nevertheless, studies regarding the diagnosis of uncertain food allergy symptoms are lacking. We examined the diagnostic decision for a food allergy based on uncertain symptoms during an Open-OFC.

Methods: We conducted an Open-OFC between August 2005 and April 2012 with 2271 cases who suspected as allergic to hen’s eggs, cow’s milk, or wheat. For the primary diagnosis, Open-OFCs with obvious symptoms were classified as “positive,” no symptoms as “negative,” and uncertain, indeterminate symptoms as “uncertain.” We encouraged the children in the uncertain group to consume the causative foods at home more than twice; if any definitive symptoms were induced, children were classified as “intolerant,” and children without any symptoms were classified as “tolerant,” for the final diagnosis.

Results: We analyzed 454 uncertain cases excluding 781 positive cases and 1036 negative cases. The symptoms that occurred for the uncertain cases included slight abdominal pain, localized skin rash, and an isolated cough. Of these cases, 362 (79.7%) were considered tolerant at the final diagnosis. Of the intolerant children at the final diagnosis, the induced symptoms at home were not serious.

Conclusions: Monitoring of recurring symptoms following consumption of causative foods at home by patients with uncertain symptoms improves the diagnostic accuracy of an Open-OFC.

KEYWORDS
allergen, food allergy, oral food challenge, pediatric

1 | INTRODUCTION

To diagnose a food allergy (FA), medical history and physical examination, skin prick tests (SPT), allergen-specific IgE (sIgE) measurements, and oral food challenges (OFCs) are useful. There are some reports about positive reactions and SPT¹⁻³ or sIgEs.⁴⁻⁵ However, to diagnose a FA accurately, an OFC is necessary.⁶⁻⁹ In the various guidelines describing an OFC, the occurrence of no symptoms during the OFC indicates a negative test result; however, the guidelines do not provide information about the manifesting symptoms,¹⁰⁻¹³ which can be uncertain. Subjective symptoms do not provide how to diagnose either.
For example, it has been suggested that 1-2 red spots around the mouth should not be of concern, without further description. Although urticaria is regarded as a positive result, there is some debate regarding whether 1-2 spots of mild hives should be considered positive. The result is more likely to be positive when subjective symptoms are reproducible or last for ≥45-60 minutes. It is particularly difficult to develop criteria for uncertain mild symptoms because the OFC results are not quantified, and the diagnosis depends on the physician.

The Practical allergy (PRACTALL) report recommends double-blind placebo-controlled food challenges (DBPCFCs) for cases that had subjective symptoms during an Open-OFC. DBPCPCs are reliable; however, it remains uncertain whether it is possible to diagnose subjective symptoms without DBPCFCs, using only Open-OFCs.

There has been no description of the final diagnostic results of cases with slight or subjective symptoms. This study used repeated consumption of challenge foods safely at home to clarify whether slight symptoms patients could take safely after an OFC.

### 2 | METHODS

#### 2.1 | The way of diagnosing oral food challenge

Symptom severity induced by the OFC was evaluated using the severity grading scale in the anaphylaxis guidelines, on a 3-point scale of "mild" "moderate," and "severe." Uncertain included mild symptoms that spontaneously resolved immediately, including <2 small wheals, erythema, or a skin rash that did not spread across different parts of the body (skin symptoms); sneezing and coughing that did not persist and unaccompanied by wheezing (respiratory symptoms); and subjective symptoms (eg, abdominal pain, nausea) that were not accompanied by objective symptoms (eg, diarrhea/vomiting) (gastrointestinal symptoms).

The severity score was based on the organ system that was most affected by the symptoms. Hypotension was defined as systolic blood pressure <70 mm Hg for children aged 1 mo to 1 y, <70 + (2 × age) mm Hg for children aged 1-10 y, and <90 mm Hg for children aged >11 y. Mild hypotension was defined as systolic blood pressure <80 mm Hg for children aged 1 mo to 1 y, <80 + (2 × age) mm Hg for children aged 1-10 y, and <100 mm Hg for children aged >11 y. Wheezing detectable via auscultation with a stethoscope was defined as mild wheezing. Audible wheezing was defined as wheezing detected without a stethoscope. This severity score was defined in the anaphylaxis guidelines for Japan.

#### 2.2 | Subjects

An Open-OFC was conducted for 2386 cases of hen’s egg, cow’s milk, or wheat allergy at the Department of Allergy, Sagamihara National Hospital, between August 2005 and April 2012. OFCs were conducted for diagnosis for the patients who were suspected FA or for confirmation of tolerance of the patients who were previously diagnosed based on a history of immediate-type reactions. OFCs were conducted at least twice for 493 patients because they had 2-3 food allergies.

| TABLE 1 Severity of symptoms during the oral food challenge |
|-----------------------------------------------------------|
| 1 (Mild) | 2 (Moderate) | 3 (Severe) |
| Skin | Localized urticaria, exanthema, wheal, pruritus | Generalized urticaria, exanthema, wheal, pruritus | — |
| | Swollen eyelid or lip | Swollen face | — |
| Gastrointestinal tract | Pruritus of the throat or oral cavity | Throat pain | — |
| | Mild abdominal pain | Moderate abdominal pain | Cramps |
| | Nausea, emesis, diarrhea | Recurrent emesis, diarrhea | Continuous emesis, loss of bowel control |
| Respiratory tract | Intermittent cough, nasal congestion, sneezing, rhinorrhea | Repetitive cough | Persistent cough, hoarseness, “barky” cough |
| | — | Chest tightness, wheezing detectable via auscultation | Audible wheezing, dyspnea, cyanosis, saturation <92%, swallowing or speaking difficulties, throat tightness, respiratory arrest |
| Cardiovascular | — | Pale face, mild hypotension, tachycardia (increase >15 beats/min) | Hypotension, dysrhythmia, severe bradycardia, cardiac arrest |
| Neurologic | Change in activity level, lethargy | “Light-headedness,” feeling of “pending doom,” somnolence, headache | Confusion, loss of consciousness, incontinence |

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allergies or were diagnosed as being intolerant during an OFC and were retested again >1 year later. Some patients were diagnosed only on the basis of increased slgE regardless of their history of consumption of suspected foods; with elevated slgE levels, we conducted the OFC. Even with patients with a medical history of an immediate reaction or anaphylaxis, the OFC was conducted if the patient had not eaten the food for ≥1 year.

Symptoms of allergic diseases such as atopic dermatitis (AD), bronchial asthma (BA), allergic rhinitis, and allergic conjunctivitis were also controlled before the OFC. AD was evaluated using a SCORAD score.

2.3 Primary diagnosis based on the oral food challenge

The physician administering the OFC made a primary diagnosis 24 hours post-OFC. The OFC was conducted according to the Japanese Pediatric Guideline for Food Allergy in the presence of a physician, nurse, and guardian, with a total intake of 1/2 a hen's egg, 50 mL cow's milk, and 16 g wheat as soft flour. The Japanese guidelines recommend reducing the total challenge dose considering the risk. The main targets were tender age, for which we chose medium doses; these volumes were sufficient for Japanese children <3 years. The challenge foods consisted of pumpkin cake made from half an egg and pumpkin, and cooked in a 1000-W microwave for 90 seconds resulting in a center temperature of 91.9°C; cow's milk as 48 g yogurt; or wheat as 50 g udon noodles. The patients consumed 5 unequal doses (1/16, 1/16, 1/8, 1/4, and 1/2 of the total amount) at 15-minutes intervals until March 2008; then, the foods were administered as 3 unequal doses (1/8, 3/8, and 1/2) at 30-minutes intervals.

Antihistamines were discontinued 72 hours before the OFC, and leukotriene receptor antagonists and other drugs were discontinued 24 hours before the OFC, in accordance with the guidelines. If positive symptoms developed during the OFC, intake of the causative food was stopped, and suitable treatment such as oral or intravenous antihistamines, intravenous steroids, inhaled beta-2 agonists, or intramuscular adrenaline was administered.

2.4 Final diagnosis for uncertain cases

The patients classified as uncertain were instructed to consume the causative foods in amounts up to the total loading dose ≥2 times in different days at home, and there were no limits as to when to eat; induced symptoms were recorded 2-4 weeks later at their outpatient visit. If the patient did not develop symptoms even after eating potentially causative food several times at home, the patient was categorized as tolerant. If the patient repeatedly developed the same symptoms observed during the OFC or developed more severe symptoms, the patient was categorized as intolerant. Repeated subjective symptoms or subjective symptoms, where it was unbearable to eat, were also categorized as intolerant.

We prospectively prescribed emergency drugs (eg, antihistamines, oral steroids) for possible severe symptoms at home. The guardians were provided specific written instructions for the response: if symptoms developed, administer the prescribed drug, observe the patient's condition, and visit the hospital if the symptoms became serious. We did not prescribe adrenaline auto–injector, unless it was already prescribed due to a history of anaphylaxis.

2.5 Statistical analysis

The values are reported as median (interquartile range [IQR]). We used t tests and chi-square tests to compare continuous and non-continuous variables between the groups, respectively. In addition to comparing the patient characteristics and symptoms, we also compared whether the symptoms developed in a single organ or multiple organs (skin, gastrointestinal tract, respiratory organ). Statistical significance was set at P < .05. Statistical analyses were conducted using SPSS v22.0 (IBM Corp, Armonk, NY).

2.6 Ethical considerations

We explained the possible symptoms induced by OFC to the guardians both orally and in writing and obtained written informed consent. This study was approved by the Sagamihara National Hospital Ethics Committee and conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Research by the Ministry of Labor, Health, and Welfare of Japan (amended, July 31, 2008).

3 RESULTS

3.1 Oral food challenge results

Of 2386 potential cases, 39 could not complete the OFC because they refused to ingest the food, and 76 were excluded because they were lost to follow-up. Therefore, we included 2271 cases (1606 patients) with OFC results that were diagnosed as uncertain (Figure 1).

3.2 Patient characteristics

The characteristics of all patients who received the OFC are shown in Table S1, and characteristics of uncertain cases are shown in Table S2. We have listed the reason why patients diagnosed as FA in Table 2.

3.3 Oral food challenge-induced symptoms and results of ingestion at home by the uncertain cases

Uncertain mild skin symptoms, respiratory symptoms, and gastrointestinal symptoms appeared during the OFC in 302 cases (n = 143, hen’s egg; n = 76, wheat; n = 83, cow’s milk), 138 cases (n = 71, hen’s egg; n = 43, wheat; n = 24, cow’s milk), and 124 cases (n = 102, hen’s egg; n = 11, wheat; n = 11, cow’s milk), respectively.

Skin symptoms were commonly induced during the home challenge in the intolerant group (n = 70, 76.1%); 13 cases (14.1%) had respiratory symptoms; and 25 cases (27.2%) had gastrointestinal symptoms (>1 symptom could be present). Almost all of the skin symptoms had actuate onset; one case experienced AD exacerbation.
These symptoms were not only same symptoms, but some patients had completely new symptoms. These newly manifested symptoms also fit the definition of “uncertain” symptoms (Table 3). Skin symptoms included localized urticaria or wheal; there was no AD exacerbation.

In the uncertain group, some cases experienced only subjective symptoms; 21 of the 22 with skin symptoms, 1 of the 2 with abdominal symptoms, and 70 of the 87 with gastrointestinal symptoms could cease elimination after the final diagnosis (87 of 101 overall). From the medical records, we confirmed that 3 cases required oral antihistamines at home. Two cases experienced localized urticaria, one of which was pruritus of the oral cavity. These symptoms were mild and were cured immediately; therefore, they did not require an emergency hospital visit.

None of the patients required adrenaline auto–injector or made an emergency visit to the hospital.

3.4 Characteristics of patients with an uncertain diagnosis

There were no significant differences in patients’ clinical background (Table 4). The sIgE levels and total serum IgE levels were also not significantly different between the tolerant and intolerant groups (Table S3).

There were similar frequencies of skin symptoms, respiratory symptoms, and gastrointestinal symptoms in the tolerant and intolerant groups (Table 5). In the uncertain group, 103 cases had multiple organ symptoms; 82 cases were diagnosed as tolerant (22.7% of tolerant group), and 21 cases were diagnosed as intolerant (22.8% of intolerant group). There were also similar frequencies of symptoms in a single organ or multiple organs.

4 DISCUSSION

4.1 Main findings

Based on the analysis regarding eating causative foods at home, we demonstrated that FA could be accurately diagnosed through an OFC. Furthermore, uncertain symptoms were tolerated by 80% of the cases. Because an FA is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food,11 reproducibility of uncertain mild symptoms should also be determined.

The guidelines recommend a DBPCFC for cases in which a general, unpleasant sensation in the oral cavity or abdominal pain without objective symptoms might be psychogenic.15 However, the results of this study indicate that monitoring for recurrence at home instead of basing the diagnosis on a single OFC might reduce the need for a blind retest.

TABLE 2 Reasons why cases were diagnosed with food allergies, in the group of patients with uncertain symptoms

| Reason                                      | Tolerant (n = 362) | Intolerant (n = 92) | Total (n = 454) | P-values |
|---------------------------------------------|-------------------|-------------------|----------------|---------|
| Atopic dermatitis and positive antigen-specific IgE | 119               | 29                | 148            | .805    |
| History of an immediate reaction with atopic dermatitis | 144               | 33                | 177            | .492    |
| Without atopic dermatitis but with a history of an immediate reaction | 95                | 30                | 125            | .222    |
| Others                                      | 4*                | 0                 | 4              | .311    |

*Three cases are positive antigen-specific IgE levels without atopic dermatitis and immediate reaction; one was due to sibling food allergy.

P-values were determined using unpaired t tests or chi-square tests, as appropriate.
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To our best knowledge, this is the first report to show whether uncertain symptoms during an OFC are definitive symptoms. It is useful to determine whether an uncertain FA is positive or negative, because some uncertain mild symptoms that are diagnosed as positive could be false positives. In addition, based on the high conversion rate from uncertain to tolerant, we believe that recurrence of mild uncertain symptoms should be monitored to improve the diagnostic accuracy of an Open-OFC. Moreover, a diagnosis with repeated intake at home after uncertain symptoms during OFC might result in unnecessary reducing the elimination of foods.

4.2 Characteristics of uncertain cases

Because of the lack of differences between the tolerant and intolerant groups in the induced symptoms and background factors, it is difficult to prospectively determine the result based on these characteristics. Skin symptoms are highly reproducible; thus, they need to be carefully assessed to eliminate other symptoms.

4.3 Safety

A high number of cases in the Intolerant group developed new symptoms at home; therefore, ceasing food elimination because of uncertain symptoms might lead to unexpected symptoms. The patients’ concerns were alleviated by providing instructions for induced symptoms and prescribing antihistamines. Three patients that used the antihistamines avoided serious symptoms and an emergency hospital visit. Furthermore, none of the patients developed severe symptoms. Therefore, safety measures such as prior prescriptions and instructions regarding when to seek medical attention are essential.

4.4 Limitations

This study has certain limitations. An Open-OFC, rather than a DBPCFC, was performed; symptoms induced by an OFC can be objective or subjective. Because the accuracy of subjective symptoms can be difficult to determine, a DBPCFC is desirable; however, an Open-OFC is also appropriate and feasible for diagnosing FA, particularly for younger patients. In the present study, 81.8% of the cases were <6 years old; therefore, we performed Open-OFCs. In the present study, there were only 8 cases in the intolerant group that were >6 years old and had only subjective symptoms.

Final diagnoses were performed by guardians; thus, false-positive results must be included in the intolerant group.

In our study, 20% of cases were uncertain, and however, the ratio of mild symptoms during Open-OFC may depend on the patient’s backgrounds; therefore, it is appropriate compared with previous reports.

### TABLE 3 Symptoms that developed at home in cases who were intolerant to causative foods

| Symptoms during the OFC | Skin symptoms | Respiratory symptoms | Gastrointestinal symptoms | Total (n = 92) |
|-------------------------|---------------|----------------------|---------------------------|---------------|
| Skin symptoms           | 55            | 2                    | 9                         | 66            |
| Respiratory system      | 14            | 7                    | 6                         | 27            |
| Gastrointestinal symptoms| 8             | 2                    | 13                        | 23            |

The total numbers might equal more than the total sample because more than 1 symptom could be experienced by each case.

OFC, oral food challenge.

### TABLE 4 Characteristics of the patients based on tolerance to the open oral food challenge

|                         | Tolerant (n = 362) | Intolerant (n = 92) | P-values |
|-------------------------|--------------------|---------------------|----------|
| Total IgE (IU/mL)       | 373.0 (88.0-1125.0) | 240.0 (73.0-771.5)  | .187     |
| Age (years)             | 3 (2-5)            | 3 (1-4)             | .538     |
| Male:female             | 233:129            | 61:32               | .728     |
| Atopic dermatitis       | 220 (60.8)         | 52 (55.9)           | .457     |
| Bronchial asthma        | 95 (26.2)          | 17 (18.3)           | .123     |
| Allergic rhinitis       | 38 (10.5)          | 12 (12.9)           | .486     |
| Allergic conjunctivitis | 17 (4.7)           | 8 (8.6)             | .133     |
| History of immediate reaction | 239 (66.0) | 63 (67.7) | .656 |
| History of anaphylaxis  | 115 (31.8)         | 34 (36.6)           | .344     |

Values are reported as median (range) or n (%).
P-values were determined using Mann-Whitney or chi-square tests, as appropriate.

### TABLE 5 Symptoms during the oral food challenge, based on tolerance at the final diagnosis

| Total challenge         | Tolerant n = 362 | Intolerant n = 92 | P-values |
|-------------------------|------------------|-------------------|----------|
| Skin                    | 236 (65.2)       | 66 (71.7)         | .235     |
| Respiratory system      | 111 (30.7)       | 27 (29.3)         | .952     |
| Gastrointestinal tract  | 101 (27.9)       | 23 (25.0)         | .577     |
| Single organ            | 280 (77.3)       | 71 (77.2)         | .972     |
| Multiple organs         | 82 (22.7)        | 21 (22.8)         |          |

The total percentage values might equal more than 100% because more than 1 symptom could be experienced.

Values are reported as n (%).
P-values were determined using unpaired t tests or chi-square tests, as appropriate.
In addition, this study was only performed in one hospital. Although only hen’s egg, cow’s milk, and wheat allergies were evaluated, we believe this method can be adapted for other foods, because the symptoms can be monitored during the OFC.

5 | CONCLUSIONS

By instructing patients with uncertain symptoms during an OFC to repeatedly eat food at home, we determined that approximately 80% of the cases could cease food elimination after the final diagnosis. Furthermore, the patients could safely ingest the foods without any severe symptoms at home. However, we could not predict the final diagnosis in patients with an initial uncertain diagnosis from background factors or symptoms during the OFC. Therefore, monitoring symptom recurrence with repeated ingestion following an uncertain diagnosis might improve the diagnostic accuracy of an OFC, avoid unnecessary elimination, and consequently improve quality of life.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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