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Oral food challenges in children

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Many patients assume that allergic reactions against foods are responsible for triggering or worsening their allergic symptoms. Therefore, it is important to identify patients who would benefit from an elimination diet, while avoiding unnecessary dietary restrictions.
The diagnosis of food allergy depends on the thorough review of the patients's medical history, results of supplemented trials of dietary elimination, and in vivo and in vitro tests for measuring specific IgE levels. However, in some cases the reliability of such procedures is suboptimal. Oral food challenges are procedures employed for making an accurate diagnosis of immediate and occasionally delayed adverse reactions to foods. The timing and type of the challenge, preparation of patients, foods to be tested, and dosing schedule should be determined on the basis of the patient's history, age, and experience. Although double-blind, placebo-controlled food challenges(DBPCFC) are used to establish definitively if a food is the cause of adverse reactions, they are time-consuming, expensive and troublesome for physician and patients. In practice, An open challenge controlled by trained personnel is sufficient especially in infants and young children. The interpretation of the results and follow-up after a challenge are also important. Since theses challenges are relatively safe and informative, controlled oral food challenges could become the measure of choice in children.

Key words: Oral food challenge, Food allergy, Child

Introduction

Adverse reactions to food are among the most common complaints in children. However, only 2-4% of these reactions can be attributed to reproducible, IgE-mediated food allergies[1]. Atopic dermatitis (AD) is commonly associated with a food allergy[2]. Gastrointestinal and respiratory symptoms may also be caused by a food allergy.

The diagnostic work-up of a suspected food allergy includes the patient's history, a skin-prick test (SPT)[3], measurement of food-specific IgE antibodies using serologic assays[4], and, more recently, the atopy patch test[5].

Since the introduction of oral food challenges (OFCs) in clinical practice, double-blind, placebo-controlled food challenges (DBPCFCs) have been used to definitively establish whether a food is the cause of adverse reactions. However, DBPCFCs are time-consuming, expensive, and troublesome for physicians and patients. An open challenge controlled by trained personnel is sufficient, especially in infants and young children[6]. This review covers the

indications, the practical performance (including preparation and dosing), and the interpretation of OFCs.

Indications for OFCs

An OFC should be performed for establishment or exclusion of a diagnosis, for scientific purposes in clinical trials, or for the determination of the threshold value or the allergenicity of foods. Fig. 1 provides an algorithm for proceeding from the suspicion of food-related symptoms to the final decision for recommending a specific therapeutic elimination diet. The process includes the measurement of specific IgE levels or an SPT in the decision-making process[6, 7]. Diagnostic decision points for specific IgE, with a 90% predictive probability for 4 major food allergens, have been described by Sampson et al. (Table 1)[4]. However, predictive decision points vary remarkably among authors and the studied population[8]. Therefore, decision points must be studied for each food allergen in the target population. These efforts may help avoid unnecessary OFCs.

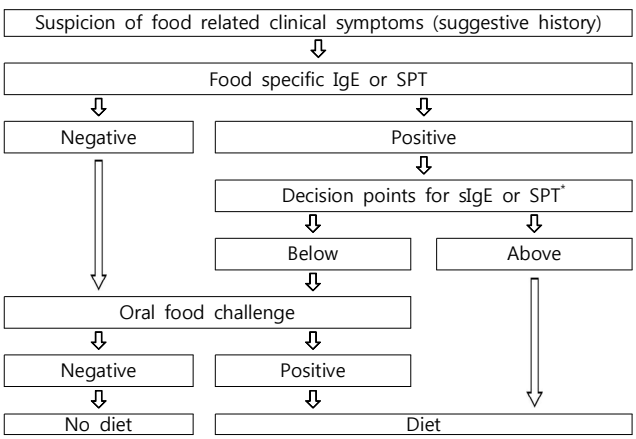

Fig. 1. How to proceed from the suspicion of food-repeated symptoms to the final decision on recommending a therapeutic specific elimination diet. *Diagnostic decision points appear to be population, age, and allergen dependent.

Table 1. Performance Characteristics of 90% Specificity Diagnostic Decision Points Generated in a Retrospective Study[13] in Diagnosing Food Allergy in 100 Consecutive Children and Adolescents Referred for Evaluation of Food Hypersensitivity

Allergen	Decision point (kU_A/L)	Sensitivity	Specificity	Efficiency	PPV	NPV
Egg	7	61	95	68	98	38
Milk	15	57	94	69	95	53
Peanut	14	57	100	84	100	36
Fish	3	63	91	87	56	93
Soybean	30	44	94	81	73	82
Wheat	26	61	92	84	74	87

Abbreviations: PPV, positive predictive value, NPV, negative predictive value

Types of OFC

There has been a debate about whether OFCs should be done in an open or double-blind fashion. In an open OFC, the food is given in its natural form. For a single-blind OFC, the food or placebo is given in a vehicle that disguises the appearance and the taste of the food. The patient is unaware of the nature of the food given, whereas staff involved in the procedure have this information. For DBPCFCs, none of the parties involved is aware of the composition of the product. Placebo challenges are indicated if day-to-day variation plays a major role in symptoms, for example in children with AD, or in cases where there are subjective symptoms such as abdominal discomfort, a burning sensation on the tongue, or palpitations[9, 10]. Common clinical indications for OFC and the corresponding procedures are shown in Table 2[10]. Although DBPCFC is generally the preferred scientific research protocol, open challenge may be indicated in infants and children younger than 3 years of age, according to a review by the European Academy of Allergology and Clinical Immunology[11].

Preparation for OFC

There are several issues to be considered prior to an OFC in patients. These can be divided into patient-related and procedure-related parameters (Table 3)[11].

1. Settings

The OFC should be designed and carried out by experienced

Table 2. Clinical Indications for Oral Food Challenges and the Corresponding Procedures

Challenge	Procedure
Anaphylaxis proven or highly probable (together with proof of specific IgE)	No oral food challenge; diet
Questionable anaphylaxis (with or without proof of IgE)	Open challenge; inpatient basis
Typical oral allergy syndrome with corresponding sensitization	No oral food challenge; diet?
No improvement of clinical symptoms under elimination (or oligo-allergenic) diet	No oral food challenge; no diet?
Introduction of new foods in sensitized infants (before exposure)	DBPCFC or open challenge*
Rechallenge after (long-term) avoidance of a food (to investigate possible acquired tolerance)	DBPCFC or open challenge*
Expected late phase clinical reactions (eg, in children with atopic eczema)	DBPCFC
Subjective symptoms (eg, abdominal discomfort, nausea)	DBPCFC

*Depending on type of symptoms (eg, presence of atopic eczema).

Table 3. Several Issues to be Determined Prior to Commencing a food Challenge in a Patient

Patient related parameters
age of the patient
clinical features of the suspected reaction
severity of the reaction
dosing (start dose, increment, top dose)
timing between challenges
regimen (in-patient or out-patient)
special considerations (concomitant factors) such as a possible influence of concomitant exercise (or intake of drugs such as β-blockers, ACE-inhibitors or aspirin, alcohol, antihistamines, corticosteroids)
Procedure related parameters
settings (trained personnel)
safety measures
informed consent procedures
blinding procedure
statistical evaluation

health care professionals in a facility where the challenge can be closely monitored and measures for the treatment of potential life-threatening reactions are available. Hospital admission or, occasionally, the intensive care unit, may be necessary in certain cases[12]. The timing, type, and severity of expected symptoms may influence the selection of the OFC location[13].

2. Food preparation

Food for an open OFC can be brought from home by the patient or parent, whereas for a blind OFC, the test material should be provided by a physician to ensure proper masking. The food should be prepared without cross-contamination or contact with other foods to which the patient may react[13]. The procedure must be adjusted according to the stability and allergenicity of the food in question[14]. Thermal processing, heating, and cooking change protein conformation and may result in a change in allergenicity [15]. Thus, tolerance to the cooked versions of many foods does not predict tolerance to less cooked forms.

The original OFC vehicle used for blinding was an opaque capsule. However, these capsules have considerable limitations: difficulty in administering adequate quantities of food, possible destruction of allergenicity, probable difficulty in swallowing, bypass of early oral symptoms, and delayed absorption[13]. Only in cases where there is a suspected reaction to additives is masking in gelatin capsules recommended[11]. For most OFCs in young children, infant formulas and applesauce are convenient vehicles[11, 13].

Dosing schedule for OFC

1. Total dose for OFCs

The total dose, that is, the maximal amount of the substance administered, should generally be the normal daily intake in a serving of the food in question, adjusted for the age of the patient. In 1 approach, the total amount administered during a gradually escalating OFC equals 8-10 g of the dry food, 16-26 g of meat or fish, and 100 mL of the wet food[16]. The challenge food is mixed with the vehicle and administered in gradually increasing increments every 15 minutes. This time interval is preferred because most acute reactions occur within 15 minutes; however, the dosing interval must be adjusted on the basis of a patient's history[11, 17]. If the patient is expected to tolerate the tested food, an age-appropriated serving of food in its natural form may be served in small potions over a period of 30 to 60 minutes (Table 4)[13].

Table 4. Examples of Portion Sizes *for an Open Food Challenge with Common Food Allergens

Food	Portion size
Milk/dairy	6-8 oz milk or infant formula
	1/2-1 cup yogurt
	1/2-1 cup cottage cheese
	1/2-1 oz hard cheese
Soy/legumes	1/2-1 cup soy beverage
	1/2-1 cup tofu
	1/2-1 cup cooked beans (kidney, pinto, chickpeas, lentils)
Egg	1 slice of French toast (1egg per l slice of bread)
	1 hard boiled or scrambled egg
Grains (rice, corn, wheat, rye, barley, oat)	1/2-1 cup pasta/rice
	1/2-1 oz cereal
	1/2-1 slice bread
	1/2-1 muffin or roll bread
Meats	2-3 oz cooked lean meat/poultry
Fish	2-3 oz cooked fish
Shellfish	2-3 oz shellfish
Peanut	30 g peanut butter = 2 tablespoons peanut butter
Tree nuts	30-40 g crushed tree nuts = 25-630 pieces
	10-15 g seeds = 1-2 teaspoons seeds
Seeds	1/2-1 cup cooked vegetable
Vegetables	1/2-1 cup leafy raw vegetable
	1 small baked white or sweet potato or 70 g french fries
	1/2-1 cup raw/cooked/canned fruit
Fruits	1/2-1 small apple/banana/orange/pear
	6-8 oz fruit juice

2. Initial challenge dose

The starting dose should be evaluated based on the patient's history and available data from the literature (Table 5)[11]. According to published data, 5% of patients react to less than 1mg of peanut, whereas 15% of milk allergic patients react to less than 5 mL of cow's milk[18, 19]. Attempts to predict the outcome of OFCs for egg, through specific IgE assays or SPT end-point titration, have also been made[20]. If possible, the initial OFC dose should be lower than the expected

Table 5. Proposed Starting Dose for Different Foods

Food	Dose
Peanut	0.1 mg
Milk	0. 1 mL
Egg	1 mg
Cod	5 mg
Wheat	100 mg
Soy	1 mg
Shrimp	5 mg
Hazelnut	0.1 mg

The actual starting dose must always be considered in the actual patient.

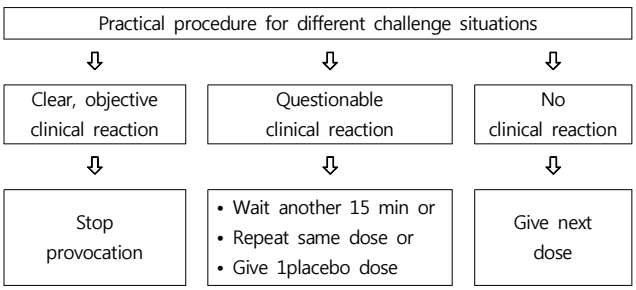

Fig. 2. Decision tree for various situations during oral food challenge procedure.

threshold dose, for example, the amount that the patient developed a reaction to previously. In an open OFC performed according to a simplified protocol, the entire serving of challenge food may be divided into 3 equal portions[13].

Interpretation of OFC

Despite controlled conditions, it is sometimes difficult to determine whether clinical symptoms are sufficiently clear to make a decision. Niggemann et al. proposed a decision tree for various situations during an OFC procedure, which is reproduced in Fig. 2[7].

Different approaches should be taken for patients presenting classical allergic symptoms with objective signs of a reaction on OFC, and for patients presenting subjective symptoms only. In a classical type I allergy with objectively measurable signs, reactions to a placebo are relatively rare and a procedure using one active OFC and one placebo is sufficient[21]. In contrast, the frequency of reactions to placebo seen in patients presenting subjective symptoms is higher. In these cases, repeated OFC is necessary[22]. Where an OFC gives a positive result, food elimination may be continued under nutritional supervision. If a negative OFC result is obtained, it is important to ensure that the quantity tolerated by the patient on the day of test corresponds to the amount likely to be eaten during a normal meal.

Risks of OFCs

OFCs should be performed in a setting suitable for the handling of any side effects, including anaphylaxis. This covers the location, the presence of trained personnel, monitoring facilities, and suitable equipment for medical intervention. Intravenous access is a basic safety measure, but complications related to such procedures have been reported, which ranged from local irritation through to thrombophlebitis of the hand or arm[23].

It is important to bear in mind the possibility of anaphylactic reaction and to recognize the initial symptoms. Such awareness of symptoms may prevent progression to a more serious clinical situation. H1 antihistamines can mask the early signs of anaphylaxis, and patients with asthma have a higher risk of anaphylaxis[10].

Conclusion

The OFC is a valuable tool in the diagnosis and management of children with suspected food allergy. In most cases, OFCs can be performed in a controlled manner without risk. Efforts to standardize OFCs, so that they enable physicians to reach better decisions and avoid unnecessary elimination diets, have been made by The Korean Academy of Pediatric Allergy and Respiratory Disease.

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