The Role of Food Allergy in Atopic Dermatitis in Children

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ABSTRACT

Atopic dermatitis (AD) patients have an increased incidence of IgE-mediated allergy to various allergens. In double blind placebo controlled food challenge (DBPCFC), the gold standard for food allergy, immediate reactions within two hours are most common but delayed reactions have also been reported. Skin prick test (SPT) and RAST test have high sensitivity but low specificity. Some authors showed that food patch test could identify patients with delayed reactions. SPT studies in Asian countries showed different results from western countries, with crustacean seafood having the highest positive rate.

Keywords: *DBPCFC, gold standard, immediate and delayed reactions, RAST, skin prick test*

INTRODUCTION

Atopic dermatitis (AD) is one of the most common paediatric skin diseases worldwide. Community study in Hong Kong suggested that the prevalence of AD among school children ranged from 3.3% in children between 13 to 14 years, to 4.2% in children between 6 to 7 years.[1,2]

Pathogenesis

The pathogenesis of AD is not yet established but an imbalance in the T-helper cells (TH) response is thought to be important. This phenomenon was first demonstrated when Reinold et al showed reduction of interferon-gamma production (TH-1 cytokine) by monocytes of AD patients.[3] Further in vitro studies had shown an increase in interleukin-4 production by T cells from atopic subjects.[4] As a result of the TH-1/TH-2 immunological imbalance, atopic subjects tend to have an aggravated immediate type but a decrease in delayed type hypersensitivity reaction.

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IgE-mediated hypersensitivity

The role of IgE-mediated hypersensitivity in the pathogenesis of AD is well documented. Over half of the patients eventually develop asthma or allergic rhinitis. Approximately two thirds of patients have a positive family history of atopy. Lastly, 80% of these children have elevated total serum IgE concentration. Indeed, patients with AD were well recognized for their increased incidence of IgE-mediated allergy to various allergens, including food and inhalants.

FOOD ALLERGY

In a recent survey of AD patients in a government clinic in Hong Kong, 44.1% of patients gave a history that food may aggravate their AD. Seafood, egg, beef, milk and fried food were the most common items quoted.[5] In the USA, 25% of the patients with AD believed that food contributed to their dermatitis.[6] However, using the one-day DBPCFC as a gold standard, authors like Bock,[7] Niggemann[8] and Sampson[9] found that history of hypersensitivity was generally of little use in predicting which patient would react to food challenge. In general, dermatologists considered that in about 10% of children, dietary factors might aggravate dermatitis.[10] However, allergists tend to put more emphasis on food. In the study by Burks, 39% of patients with AD showed positive reaction to one or more food in DBPCFCs.[6]

Definition

Food allergy is a term applied to a group of disorders characterized by abnormal exaggerated immunological response to specific food proteins. It occurs more frequently among patients with AD. DBPCFC has become the gold standard for the diagnosis of food allergy since its development by Bock and May in 1978.[7] Two types of food allergy are now recognized among patients with AD – immediate and delayed food allergies.

Immediate reactions

It is the most commonly reported type of reaction and is defined as the occurrence of skin itchiness or rash, respiratory or gastrointestinal symptoms within two hours after taking the food capsules. Symptoms of more than one organ system may occur. Skin reactions were most common, accounting 80% of positive challenge.[8,11] It presented as pruritus, diffuse erythematous macular, maculopapular or morbilliform rash, and occurred most commonly in the areas where eczema typically flared. Urticarial lesions were uncommon.[11] Gastrointestinal symptoms of nausea, abdominal pain, vomiting, and diarrhoea occurred in 27-52%. 13-32% developed respiratory symptoms such as nasal congestion, sneezing, wheezing and stridor.[6,11]

Delayed reactions

Besides the immediate reactions, the delayed type of reaction was recently identified. These reactions occurred more than two hours after the challenging food had been taken. The symptoms are identical to those of immediate reactions. While some studies[12,13] found no late reactions after DBPCFC, Niggemann[8] reported that cutaneous late reaction occurred in 25%, combined early and late cutaneous reactions in 5% and immediate reaction alone in 70% of positive reactions. Sampson reported that late reactions did not occur without early reactions.[11]

Mechanism

Sampson had demonstrated that patients experiencing symptoms after oral food challenge had a significant rise in their plasma histamine levels, whereas there was no change in asymptomatic patients.[14] Patients with AD and food hypersensitivity were found to have a higher rate of spontaneous release of histamine from basophils. Their mononuclear cells produced a histamine-releasing factor in vitro that provoked the release of histamine from the basophils of other food-sensitive persons. Both abnormalities decreased after a period of elimination diet.[15] Skin suction blister model study had shown a biphasic rise of histamine in lesions after food challenge with the relevant foods, indicating that mast cells might be responsible for early reaction and basophils for late reaction.[16]

Some recent studies produced evidence of cell-mediated immunity being involved in food allergy. Kondo had shown an increased interleukin-2 activity and interferon-gamma concentrations in culture supernatants of ovalbumin-stimulated peripheral blood mononuclear cells from patients with AD who were sensitive to hen's egg.[17] The production of a lymphokine, the leukocyte-migration-inhibition factor (LIF), by peripheral blood lymphocytes in response to an in vitro challenge with bovine β-lactoglobulin was shown to be significantly elevated in all patients with cow's milk allergy.[18]

Foods involved

Various studies in the USA, Germany and Japan showed that milk, egg, fish, wheat, soy and peanut were the common causes of clinical allergy while shellfish was not a common allergen.[6,8,11,13,19] These six foods accounted for 90% of the positive clinical response.[14]

INVESTIGATIONS

Double-blind placebo-controlled food challenge

Methods

Since the development of DBPCFC, it has been well recognized as the gold standard for food allergy. Book[20] and Niggemann[21] have also given detailed outline of their techniques. When the dehydrated foods were not available commercially, they could be prepared by the dehydration method. The raw food was dehydrated by the freeze-drying machine, ground into fine powder with an electric blender, and finally encapsulated with machine so that each capsule contained an identical weight of content.

Both patients and observers were blinded. Patients were advised to avoid the tested food for a period of two weeks. They received either the dehydrated food capsule or the placebo of sucrose capsules in the

morning and the other one in the afternoon. Patients were kept in the ward for one day for observation of reactions and resuscitation in the rare cases of severe reactions or anaphylaxis. Capsules were given in increasing amounts with 15 minutes between doses until a total dose of 15 grams had been given. Any skin, gastrointestinal and respiratory symptoms of food allergy were recorded in a standardized chart.

Open challenge

If no immediate reaction were detected at the end, an open food challenge with the food would be given as a meal in the hospital. Occasionally, DBPCFC response may show discrepancy from open challenge because the amount of allergen may differ or the allergen in open challenge may be destroyed during cooking. In a study on beef allergy, three of the eleven patients who had reactions with raw beef were able to tolerate well-cooked beef. Specific IgE to heat-labile beef proteins were found in their sera.[22] However, cases diagnosed by open challenge were generally considered less reliable because it was subjected to placebo effects.

Skin prick test

Prick tests are often used as a guide to choose the food for DBPCFC. Positive SPT was very sensitive in predicting immediate reactions in DBPCFC. However, only 30-40% of patients with positive SPT showed clinical reactions on food challenge.[12] Burks showed that a child with AD would be most unlikely to have food allergy if he had negative SPT results for all the seven most common allergenic foods.[6]

Methods

SPT may be performed with a commercially available set of standard solutions of the common food allergens including 20 to 30 food items. A 1-mm, one-peak lancet was used and prick testing was done on the volar aspect of the forearm. The investigator would assess the test sites after 15 minutes, a weal with diameter of 3 mm or larger was taken as positive. Normal saline and histamine were used as negative and positive controls respectively. No antihistamine was allowed for at least 72 hours before the SPT.

Foods involved

Table 1 summarized the frequencies and patterns of positive SPTs in different countries. In the West, egg, wheat, peanut, soy, milk and fish were the most common items with positive SPT, whereas in the Asian countries, shellfish had the highest incidence of positive SPT or elevated specific IgE.

The local study of adult asthmatic patients by Leung et al showed that, royal jelly had the highest SPT positivity prevalence of 16.8%. Shellfish and egg yolk were the next highest, about 12% each.[24] However, DBPCFC on shellfish had not been done in Asia. In a study in Taiwan, 30 atopic children with both histories of cow's milk allergy and positive RAST tests received DBPCFC with cow's milk. All of them showed negative challenge results.[25] In Singapore, a retrospective study of food-induced anaphylaxis showed that the most common food-allergic source was the Chinese delicacy bird's nest soup, followed by crustacean seafood, egg and cow's milk. In contrast to the reports of the USA, there was a notable absence of peanut or tree nuts triggering reactions. Therefore, besides having different SPT results, Asian population also showed different clinical pattern.[26]

Sensitivity and specificity for prediction of immediate reactions

As shown in Table 2, western studies indicated that the negative predictive accuracy of all the foods studied were very high, so that a negative SPT almost ruled out the possibility of a positive food allergy which would be demonstrated by an immediate reaction of the DBPCFC. Howover, the positive predictive accuracy varied amongst different foods: wheat and shellfish had a low positive predictive accuracy of less than 30%.

The discrepancy between allergenicity and antigenicity of food had been explained by changes in permeability of the intestine and neutralization by IgA in the intestinal mucosa and serum. In fact, studies had shown that some of the children with food allergy might gradually lose their clinical hypersensitivity but maintained their SPT positivity.

Rast test

Radioallergosorbent test (RAST) is a radio-immunoassay blood test used to detect IgE antibodies to specific antigens. Sampson[12] had shown that when tested with DBPCFC, SPT and RAST results had very similar sensitivities and specificities, and employing both SPT and RAST did not give additional information. The study in Taiwan also showed high concordance between the two tests.[29] It is more expensive than SPT. However, it does not carry the risk of an allergic reaction

Table 1. Frequency and pattern of positive SPT in different areas

	Sampson & McCaskill[12]	Burks & Mallory[13]	Guangzhou (Lai et al)[23]	Hong Kong (Leung et al)[24]	Japan (Iikura)[20]	Thailand[20]	Philippines[20]	Singapore[20]	Taiwan[25]
Patient characteristic	113 severe AD children	46 mild to severe AD children	763 patients with asthma	666 adults with asthma				atopic>5, prick test or serum IgE	30 AD children
Egg	55	8	7.2%	yolk 12.5% white 7.7%	46	29	12	22	13%
Peanut	49	6		6.4%	1	42	8	14	33%
Soy	34	1			8	33	6	11	33%
Milk	26	4	10.4%	4.1%	17	20	12	23	13%
Wheat	15	2			11	NE	15	19	37%
Fish	29	2		6.9%	9	NE	24	NE	17%
Chicken	19	1							
Beef	18	0	14.9%						
Pork	32	0							
Corn	7	0							
Chocolate	4	0							
Cashew		0							
Pea	19								
Shrimp	18		70.3%						43%
Rice	8				4	33	NE	NE	
Tomato	5								
Green bean	7								
Rye	8								
Oats	7								
Strawberry									
Crab			60.8%						47%
Squid			37.7%						
Royal jelly				16.8%					
Shellfish				12.1%	Negative	43	22	50	
Crayfish			42.1%						
Lobster									

Table 2. Skin prick test – variation of predictive accuracy with food

	Sampson & Ho[27]		Bock & Atkins[28]	
	Positive predictive accuracy	Negative predictive accuracy	Positive predictive accuracy	Negative predictive accuracy
Egg	0.85	0.90	0.75	0.95
Peanut	0.55	0.75	1.00	1.00
Milk	0.66	0.93	0.64	0.89
Nuts			0.45	1.00
Wheat	0.35	0.94	0.27	1.00
Soy	0.35	0.84		
Fish	0.77	0.80		
Fish and shellfish			0.25	1.00

and is useful when SPT cannot be performed due to diffuse dermatitis or dermatographism, or when antihistamines cannot be discontinued. In recent years, a modified RAST test called the CAP system FEIA (Pharmacia Diagnostics, Uppsala, Sweden) had been developed.[27] It provided a quantitative assessment of allergen specific IgE antibody. The diagnostic levels of IgE for egg, milk, peanut, and fish allergies had been identified, which had a predictive value of over 95%.[27]

Patch test

Patch test is not a standard or commonly used test for the diagnosis of food allergy. Isolauri[30] and Kekki[31] studied on cow's milk allergy in infants with atopic dermatitis. They used suspension of milk powder in normal saline for patch test and demonstrated that while many patients with immediate reactions were detected by SPT, patch testing could identify others with delayed reactions. Besides, Kekki showed that 26% of the cow's milk allergic infants were detected by patch test only, so that it improved the accuracy of skin tests in the diagnosis of food allergy in infants with atopic dermatitis. Majamaa in Finland reported that for both wheat allergy and cow's milk allergy, delayed-onset reactions were more common than immediate skin reactions and a higher percentage of allergic patients was detected by patch test than SPT.[32,33]

Breneman developed a food patch test using a suspension made of sterile, freeze-dried food products in Dimethylsulfoxide (DMSO).[34] This test is called Dimethylsulfoxide Food Test (DIMSOFT). He found that while DBPCFC immediate reactions correlated well with the RAST test positive results, the delayed reactions correlated only with the positive DIMSOFT test. The sensitivity was 74.4% while the specificity was 34.0%. No systemic adverse effects had occurred in his series of 400 patients with DIMSOFT test.

Biopsies at the positive sites had demonstrated an increase in T-lymphocytes, IgE, IgG, IgM, C3 and C4, suggesting that besides Type I reaction, other types of Gell-Coombs' immune reactions to food antigens were also in play.

Food aggravation of atopic dermatitis

Positive reactions in DBPCFC was usually regarded as diagnostic for food-induced aggravation of the AD. The study of Engman in 1936 was frequently quoted.[35] A child with documented sensitivity to wheat had half of his body protected by dressings before oral challenge with wheat. Within two hours, the child developed intense pruritus, resulting in vigorous scratching of exposed areas. Eczematous lesions appeared only on exposed sites. However, it only involved a single patient. It did not tell how often this may occur, and whether aggravation could occur without immediate reaction. While scratching may be one of the mechanisms for aggravation, other authors had proposed late-reaction and type IV reactions as possible alternative mechanisms. Furthermore, in the studies on the effect of food on the severity of AD, interpretation was difficult. Different authors gave their own arbitrary definitions of aggravation and their results were conflicting.

Definition of significant aggravation

In the controlled trial of a few foods diet (eliminating all but 5-8 foods) in AD patients by Mabin, a change of over 20% of the baseline score was arbitrarily defined as significant.[36] Reekers arbitrarily defined an increase of 30 SCORAD points as positive.[37] Moneret-Vautrin did not mention about the score criteria of positivity.[38] In the population study of food intolerance by Young, the severity and frequency of symptoms were recorded on a scale of 0-3 points. Cut-off points for the differences between scores during placebo period and challenge period of 5 or 3 points were chosen arbitrarily to incorporate definite cases or probable cases respectively.[39]

Improvement of atopic dermatitis with diet management

In the study of Sampson on 113 severe AD children, 56% of patients had one or more positive immediate response to DBPCFC.[15] Three years after their food challenge study, the group of 13 children with elimination of identified allergenic food had much better clinical improvement than the group of 14 children without food elimination.

Atherton performed a double-blind controlled crossover trial of an egg and cow milk exclusion diet in 36 children with AD.[40] Twenty completed the study. Fourteen patients (70%) responded more favorably to the antigen-avoidance diet than to the control diet, whereas only one (5%) responded more favorably to the control diet. Furthermore, there was no correlation between a positive SPT of egg and cow milk antigen and response to the trial diet. However, a very similar

study by Neild showed a much less striking overall response rate of 25%.[41]

Mabin studied 85 children with refractory AD. They were divided into three groups, receiving a few foods diet supplemented with either a whey hydrolysate or a casein hydrolysate formula, or to remain on their usual diet and act as control for a six-week period. They failed to show benefit from a few foods diet.[36]

Practical approach on suspected food allergy in atopic dermatitis

Both Bock and Sampson suggested that because of the high sensitivity and low specificity, skin prick test should be used not to diagnose food allergy but to identify subjects in whom DBPCFC are required.[10,42] Burks suggested that any child with AD, which did not respond satisfactorily to first line conventional treatment, should be screened for food allergy with SPT, and then open food challenge for positive items. Patients with a food having more than three positive food challenges may then undergo a DBPCFC for that food.[6] Other authors had suggested various slightly different protocols.

CONCLUSION

Although many AD patients believed that food might aggravate their skin condition, the history was unreliable for diagnosis. Many tests have been used to identify the role of food allergy in AD. Skin prick test and RAST test are useful for screening. Some authors found food patch test useful. DBPCFC remains the gold standard. Studies on the effect of food on the severity of AD showed conflicting results.

Learning points:

DBPCFC is the gold standard for diagnosis of food allergy. SPT and RAST have high sensitivity but low specificity, and is therefore useful only for screening. History of food-induced aggravation of AD is generally unreliable.

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