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The Necessity of Diet Therapy for Successful Interferon-γ Therapy in Atopic Dermatitis

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The avoidance of incriminated foods is one of the principal therapies for atopic dermatitis (AD). Recently, interferon (IFN)-γ therapy has been tried in AD with limited success. The necessity of diet therapy for the success of IFN-γ therapy in AD was evaluated. A total of 524 AD patients participated in this study and 316 patients among them were entered into open food challenge tests. As the first step, an elimination diet was administered to 43 AD patients and 30 AD patients were enrolled as an untreated control group. As the second step, 45 AD patients were treated by both IFN-γ therapy and elimination diet alone, 30 AD patients by elimination diet alone, 50 AD patients by IFN-γ therapy, and 43 AD patients as controls. Clinical severity reduced significantly by using only the elimination diet in 58.1% patients with varying degrees of AD. Elimination diet improved the clinical results of IFN-γ therapy in AD. In regard to the food challenge test, 77.8% of AD patients showed an adverse reaction to at least one food. Diet therapy itself had therapeutic effects on AD and an elimination diet might be essential for the success of IFN-γ therapy in AD.

Key Words: Atopic dermatitis, Interferon-gamma, elimination diet, open food challenge

INTRODUCTION

Atopic dermatitis (AD) is a skin disease due to immune dysregulation,[1] although the role of allergy is controversial in the disease.[2] The conventional treatments for AD comprise the use of emollients, steroids, sedating antihistamines at night, antibiotics, and the avoidance of irritating detergents or clothing.[3] However, with even the most devoted applications of these measures, a number of patients still suffer from this persistent and troublesome disease. Immunosuppressive drugs such as cyclosprorin A,[4] and immunomodulatory therapy of interferon (IFN)-γ,[5] IFN-α,[6] thymopentin,[7] and intravenous immunoglobulin (IVIG)[8] have been tried. IFN-γ therapy in AD has been tried with limited success. There have been frequent symptomatic fluctuations during therapy and rapid recurrences after therapy.[9] Therefore, the use of INF-γ therapy has waned due unsatisfactory clinical results such as a low response rate, a high recurrence rate, frequent symptomatic fluctuations, high cost, and considerable time consumption.

Although there is no consensus concerning the role of food allergy in the etiology of AD,[10] it has been demonstrated that food hypersensitivity played a pathogenic role in a significant number of children who had AD. The appropriate identification of food hypersensitivity and subsequent exclusion diets can lead to significant improvements.[11,12] To address this controversy, the clinical effects of an elimination diet in AD were evaluated in the first step of this study. In the second step, the therapeutic effects of an elimination diet in IFN-γ therapy of AD were investigated. Some investigators have suggested the supply of an elemental diet as an initial dietary manipulation in AD.[13] While others have suggested an elimination diet.[14] In this study, the process of the elimination diet was modified for the convenience and compliance of patients. The effectiveness of these elimination diet processes was verified. A properly performed double-blind, placebo-controlled food challenge (DBPCFC) has been shown to be the only accepted test for the confirmation of the

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diagnosis of adverse reactions to food.[15,16] However, the validity of an open food challenge test has proven to be convincing for the food challenge method.[17] Additionally, the usefulness of a careful history taking of food allergy, skin prick test, and specific IgE detection have been statistically described by comparing open food challenge test results.

MATERIALS AND METHODS

Patients and study design

A total of 524 atopic dermatitis (AD) patients (M:F=254:270; mean age=13.7 ± 14.4) who visited the AD clinic of Samsung Cheil Hospital and Seoul Allergy Clinic, Seoul Central from May 1, 1997 to June 30, 2000 were enrolled in the study. They fulfilled the criteria of Hanifin and Rajka,[18] and had suffered from AD for over six months. A detailed history was obtained with special attention to food intake and its possible relation to AD exacerbation. Elemental laboratory examinations including complete blood count (CBC), total eosinophil count and total IgE levels, were conducted in all patients.

Grading the clinical severity of AD was assessed by the scoring system of Hanifin and Rajka.[18] The total clinical severity score (range from 0 to 15) was defined as the sum of five individual scores - pruritus, erythema, edema/papulation, excoriation, and scaling/dryness - which were graded as 0 (none), 1 (mild), 2 (moderate) and 3 (severe). The distribution of the clinical severity scores in this study were as follows: clinical severity score from 1 to 3 - 80 subjects; clinical severity score from 4 to 6 - 221 subjects; clinical severity score from 7 to 9 - 93 subjects; clinical severity score from 10 to 12 - 80 subjects; clinical severity score, from 13 to 15 - 50 subjects. Systemic steroid or other medications were tapered off and withheld for at least 1 month before entering the study. Only topical steroid application of 1% hydrocortisone was allowed. Upon entrance into the study, a detailed medical history and physical examinations were obtained. The past history concerning food allergy was carefully recorded in all patients. No patient possessed a convincing history of a major anaphylactic or anaphylactoid reaction. Patients or parents were informed about the study on their initial visit and all studies were approved by Ethics Committee of Samsung Cheil Hospital.

In the first step, the effectiveness of the elimination diet as a dietary manipulation method was verified. An elimination diet was administered 43 AD patients as described below. Furthermore, as a control group, 30 patients were enrolled without any treatment. In the second step, the clinical significance of diet therapy in the IFN-γ therapy of AD was investigated. Another 30 AD patients were treated only by diet elimination. Fifty AD patients were treated with only the IFN-γ therapy as described below. Another 43 AD patients were enrolled as control subjects. Forty-five AD patients were treated with a combination of IFN-γ therapy and elimination diet. Open food challenge tests were conducted on 316 AD patients in order to confirm food allergies.

MAST, FAST and skin prick test

All patients were tested with MAST (MAST Immunosystem, Inc., Mountain View, CA, USA) and fluorescent allergen-sorbent-test (FAST) (Bio-Whittaker, Inc., Walkersville, MD, USA) for the identification of specific IgE for food allergens. The test allergens are listed in Table 1. MAST and skin prick tests were performed routinely. The allergen items that were positive in the skin prick test and absent in the items of MAST, were compensated by FAST. The MAST and FAST assays were done according to the manufacturers instructions.

Skin prick tests were conducted on the backs of all patients using commercially available allergens (Torii Pharm. Co., LTD, Tokyo, Japan; Bencard, Brentford, England) as listed in Table 1. Histamine hydrochloride 1 mg/ml (Bencard) was used as a positive control. Pricking with the vehicles (physiologic saline and distilled water) was the negative control. Reactions were read after 15 min and classified as negative (0: no reaction, 1+: reaction greater than control reaction but smaller than half the size of histamine) or positive. Positive reactions were graded as follows: 2+: half the size, 3+: equal to, and 4+: twice as large as the

Table 1. Test Results of Past History, Skin Prick Test and Specific IgE. Percentage (positive count) of Total 524 Atopic Dermatitis Patients

Foods	Past History	Skin Prick Test	Specific IgE
Rice	0 (0)	6 (34)	5.8 (14)
Wheat	2.1 (11)	68 (356)	26 (62)
Corn	0 (0)	0 (0)	5.8 (14)
Rye	0 (0)	37 (192)	11 (27)
Barley	0 (0)	36 (189)	9.1 (22)
Mixed Beans	0 (0)	26 (138)	0 (0)
Peas	0.2 (1)	27 (140)	5.4 (13)
Soybean	2.5 (13)	23 (121)	49 (119)
Peanut	1 (5)	46 (243)	14 (33)
Almond	0.4 (2)	38 (200)	9.1 (22)
Walnut	1.1 (6)	22 (116)	5 (12)
Hazelnut	0 (0)	33 (172)	8.3 (20)
Beef	2.1 (11)	50 (262)	41 (100)
Pork	21 (110)	40 (209)	41 (98)
Lamb	0.4 (2)	32 (168)	1.2 (3)
Chicken	23 (118)	37 (195)	32 (77)
Mackerel	9.2 (48)	21 (109)	0.8 (2)
Tuna	1.5 (8)	68 (358)	15 (36)
Herring	0.8 (4)	23 (126)	0 (0)
Sardine	0 (0)	24 (126)	0.4 (1)
Plaice	0.2 (1)	25 (129)	0.4 (1)
Codfish	0.2 (1)	48 (249)	15 (35)
Salmon	0.2 (1)	32 (167)	4.1 (10)
Egg	16 (85)	48 (254)	58 (140)
Milk	12 (62)	54 (281)	64 (154)
Cheese	1.9 (10)	43 (227)	20 (47)
Crab	4.4 (23)	40 (207)	35 (85)
Robster	0.4 (2)	52 (274)	2.5 (6)
Clam	2.7 (14)	52 (270)	0.8 (2)
Mussel	0 (0)	29 (153)	0.4 (1)
Shrimp	2.7 (14)	57 (297)	28 (68)
Oyster	0.4 (2)	41 (213)	0.4 (1)
Strawberry	0.8 (4)	26 (134)	3.7 (9)
Banana	0.4 (2)	25 (132)	5.8 (14)
Orange	1.3 (7)	22 (114)	6.6 (16)
Melon	1.5 (8)	0 (0)	0 (0)
Pear	0 (0)	0 (0)	0 (0)
Peach	4.6 (24)	27 (141)	20 (48)
Tomato	8.8 (46)	42 (222)	10 (25)
Grape	0.2 (1)	28 (148)	5.4 (13)
Lemon	0 (0)	27 (140)	7.5 (18)
Apple	0.8 (4)	23 (120)	8.3 (20)
Parsley	0 (0)	34 (176)	3.3 (8)
Celery	0 (0)	43 (227)	8.3 (20)
Mushroom	0 (0)	56 (292)	0.8 (2)
Cabbage	0 (0)	36 (191)	4.1 (10)
Spinach	0.2 (1)	39 (203)	5 (12)
Potato	0 (0)	27 (143)	5.4 (13)
Onion	0.4 (2)	26 (138)	11 (26)
Garlic	0.2 (1)	0 (0)	5.4 (13)
Carrot	0.2 (1)	26 (135)	6.6 (16)
Lettuce	0 (0)	46 (240)	0.4 (1)
Sesame	0.2 (1)	46 (243)	0 (0)
Chocolate	2.1 (11)	48 (251)	10 (25)
Malt	1.5 (8)	31 (163)	0 (0)
Yeast	0.4 (2)	39 (205)	13 (32)
Tea	0 (0)	29 (153)	0 (0)
Coffee	0.2 (1)	34 (180)	0.4 (1)

size of histamine. The minimum size of a positive reaction was 3 mm.

Elimination diet with replace diet and open food challenge test

Patients were asked to eliminate the suspected foods according to the results of past history, skin prick test, and specific IgE (maximum elimination phase). Replacement diets to provide substitutes for the foods to be eliminated were supplied during the elimination diet for a balanced nutrition (Table 2). To confirm the complete elimination of all foods identified as allergens, dietary diaries were recorded by all patients. The analysis of dietary diaries was performed by special dietitians and a physician.

Open food challenge tests[17] were performed according to the following indications (challenge phase): 1) Obvious clinical improvement was obtained and the patients clinical status was stable for at least 2 weeks. Particularly during IFN-γ therapy, open food challenge tests were conducted for two weeks following the first injection; and 2) Allergens that were planned to be tested were completely eliminated in the diet. This was checked by the analysis of the dietary diary by a special dietician. To exclude possible environmental factors, patients maintained their living patterns as regularly as possible during the test period.

Open food challenge tests were conducted in two steps by gradually increasing the amount day by day (Table 3). Patients consumed the foods once per day in the morning. Three days following the first challenge, the clinical result of the food challenge and the severity score were evaluated. If patients showed increased severity scores or an obvious aggravation of clinical symptoms or signs, the tests were stopped. Otherwise, the food challenge tests were continued with increased quantities of the challenged food for another 4 days. If patients showed aggravated symptoms by in the test, the next challenges were delayed until patients recovered to the pre-challenge state. When patients consumed the food that was to be eliminated during the study, the challenge tests were stopped and the patients were observed for 1 week. Thereafter, only foods incriminated by a positive challenge were com-

Table 2. Elimination Food & Replacement Food

Elimination food	Replacement food	Food product	Food group
Wheat	Rice	Rice, Glutinous rice Rice cake, etc.	Cereals & Cereal products
	Potato	Potato, Potato starch, etc.	
Soybean	Seaweed	Laver, Sea mustard Sea tangle, Sea lettuce, etc.	Supplement of calcium
	Dried fish	Anchovy boiled-dried, Icefish dried strip, etc.	
	Vegetable	Red pepper leaves, Radish leaves, Mustard leaf, etc.	
Beef	Fish	Mackerel, Cod, Herring Tuna, etc.	Supplement of protein
Pork	Beef	Beef Mackerel, Cod, Herring Tuna, etc.	Supplement of protein
Chicken	Beef, Fish	Beef Mackerel, Cod, Herring Tuna, etc	Supplement of protein
Mackerel	Fish	Salmon, Cod, Herring, Tuna, etc.	Supplement of protein
Egg	Soybean	Soybean curd, Unpressed soybean curd Soybean sprout, etc.	Supplement of protein
Milk	Soybean	Soybean milk	Milk & Milk products
Sesame	Oil	Olive oil, Corn oil, Soybean oil, etc	Oils

Table 3. Food Increased Unit in Food Challenge Testing

Test Food	Food Products	1 Portion	Increase (g)
Wheat	Noodle	90 g (1/2 cup)	90, 180, 270
	Bread	35 g (1 slice)	35, 70, 105
Soybean	Soybean curd	80 g	80, 160, 240
	Soybean milk	100 ml	100, 200, 400
Meat	Beef, pork, Chicken	40 g	40, 80, 120
Mackerel	Mackerel	50 g	50, 100, 150
Egg	Egg	50 g (one)	50, 100, 150
Milk	Milk	100 ml	100, 200, 400
Sesame	Sesame oil &	1tea spoon (ts)	1 ts, 2 ts, 3 ts
	Sesame seeds	1tea spoon	1 ts, 2 ts, 3 ts
Chocolate	Chocolate	20 g	20, 40, 60

pletely eliminated (minimum elimination phase).

Interferon therapy with or without elimination diet

Fifty patients were treated with IFN-γ therapy only and 45 patients were treated with IFN-γ therapy combined with an elimination diet. Patients received only subcutaneous injections of 2×10^6 IU/m^2 recombinant interferon-γ with specific activity of 2×10^7 IU/mg (LG Chemistry,

Seoul, Korea). Injections were given 3 times per week for 2 weeks followed by 2 injections per week for 6 weeks. Patients were instructed to take oral acetaminophen (10 mg/kg, up to a maximum dose of 600 mg) 1 hour before injection and 4 hours after injection in order to reduce possible unwanted effects, including a febrile reaction.

Statistical analysis

Analysis was performed using the statistical package SPSS Version 7.0 The data is shown as the mean ± standard deviation. The sensitivity and specificity were also calculated. In order to evaluate the significance of the test, a statistical analysis was performed. The correlation, linear regression, and paired t-test were used in this study. Differences associated with a probability of $P < 0.05$ were considered significant.

RESULTS

Effects of elimination diet in AD

The reduced mean clinical severity scores shown in the AD group that underwent an elimination diet process (n=43; M:F=20:23; mean age, 14.0 ± 17.2 years), from 6.4 ± 2.9 to 3.8 ± 3.0 ($p < 0.001$), were noticeable, while those of the AD group that did not go through the process (n=30; M:F=15:15; mean age, 17.8 ± 18.9), from 6.3 ± 1.8 to 5.6 ± 1.9 ($p > 0.05$), were not significant (Fig. 1). The initial mean clinical severity scores of the two groups did not differ from one another (p=0.184). By elimination diet, 4 patients (9.3%) showed complete clinical remission, 21 patients (48.8%) improved more than 20%, 10 (23.3%) improved less than 20%, and 8 (18.6%) showed no clinical improvement. Out of the 4 patients who showed complete remission, 3 were under the age of 5. That is 27.3% of a total of 11 patients belonging to the same age group. Another patient who showed a complete remission belonged to the group '5 years of age or over' and this comprises 3.1% of a total of 32 patients. Of the 8 patients who showed no clinical improvements whatsoever, 1 patient (9.1%) belonged to the age group 'under 5' (n=11), and 7 patients (21.9%) were from the group '5 years of age or over' (n=32).

WBC counts were unchanged in the diet therapy group and the control group (data not shown). The total eosinophil counts of the diet therapy group were reduced from 454.5 ± 233.7 counts/ml to 335.1 ± 106.7 counts/ml ($p < 0.01$) compared to those of the AD control group from 372.6 ± 256.8 counts/ml to 428.6 ± 381.7 counts/ml ($p > 0.05$). The serum total IgE levels of the diet therapy group (from 1342.3 ± 1371.5 IU/ml to 1527.2 ± 1241.5 IU/ml, $p > 0.05$) and the control group (from 1641.3 ± 1466.4 IU/ml to 1599.4 ± 1479.7 IU/ml, $p > 0.05$) showed no significant changes.

The initial severity scores and the improved extent showed a significant negative correlation with the elimination diet (R^2=0.233, p=0.001; Coef = -0.482) (Fig. 2a). Conversely, the initial severity scores were positively correlated with the final severity scores significantly with the elimination diet (R^2 = 0.760, p = 0.0001, Coef = 0.872) (Fig. 2b).

Effects of elimination diet on interferon-γ therapy in AD

As expected, diet therapy improved the clinical results of IFN-γ therapy in AD (Fig. 3). Using diet restriction only, 3 patients (10.0%) showed complete clinical remission, 14 patients (46.7%) improved more than 20%, 8 (26.7%) improved less

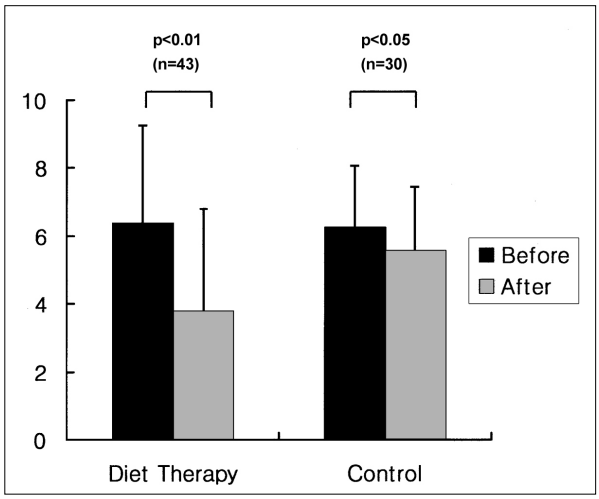

Fig. 1. The therapeutic effects of an elimination diet in atopic dermatitis (AD). Before: before therapy, After: after therapy. Diet therapy group: AD group with elimination diet; Control group: AD group without any therapy.

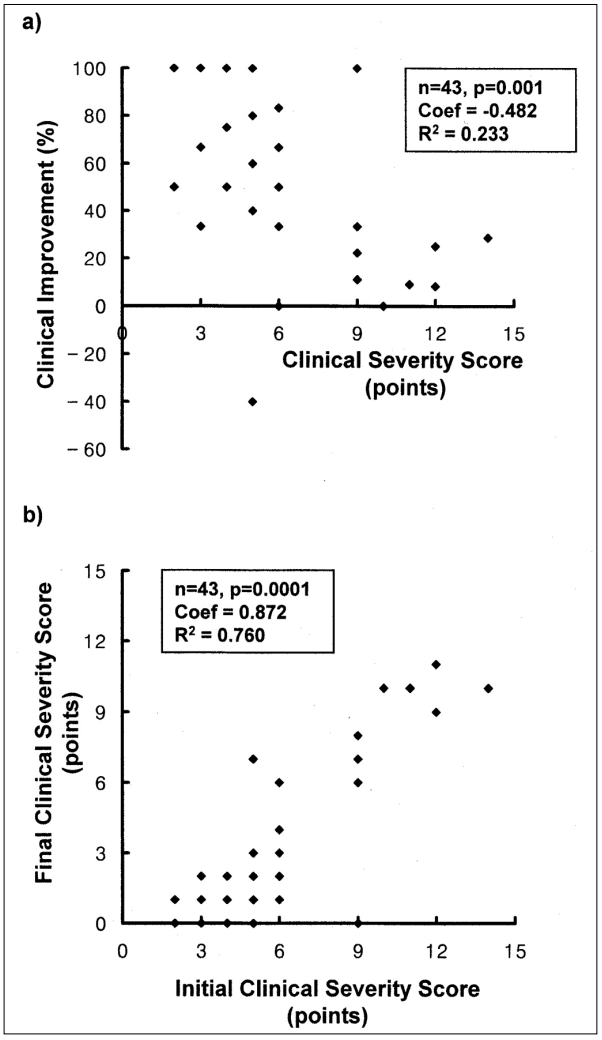

Fig. 2. The characteristics of the clinical response using the elimination diet. a) The correlation between the initial clinical severity score and the degree of clinical improvement. They showed a significant negative correlation. b) The correlation between the initial clinical severity score and the final clinical severity score. These showed a significant statistically positive correlation.

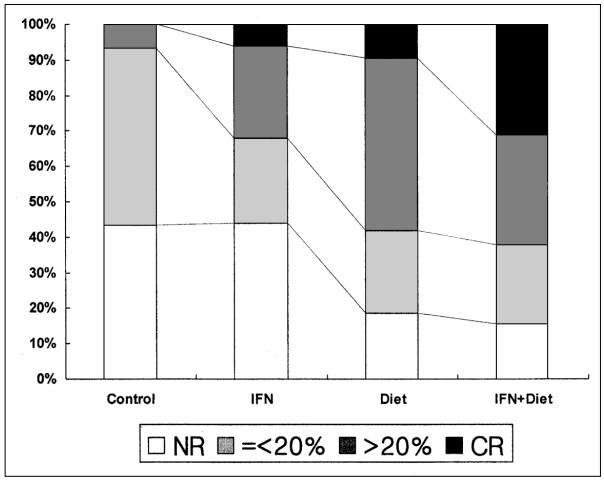

Fig. 3. Comparison of clinical results by interferon (IFN)-γ, diet, and IFN+diet therapy. Control: control group without any therapy; IFN: IFN-γ therapy group; Diet: diet therapy group; IFN+Diet: IFN-γ plus diet therapy group; CR: complete remission; >20%: improvement of more than 20%; =<20%: improvement of less than or equal to 20%; NR: no response.

than 20%, and 5 (16.7%) showed no clinical improvement (Fig. 4). Of the 3 patients who showed complete remission, 2 were from the age group 'under 5'. A total of 10 subjects were tested from this age group and this made up 20.0% of that group. The remaining 1 patient was from the age group '5 years or older'. A total of 20 subjects were tested from this group making it 5.0%. Among the 5 patients who showed no clinical improvements whatsoever, 1 belonged to the age group 'under 5' (10.0% of a total of 10 subjects tested in this group) and 4 belonged to the age group '5 or over' (20.0% of a total of 20 subjects tested in this age group).

By IFN-γ therapy, 3 patients (6.0%) showed complete remission, 13 (26.0%) were improved more than 20%, 12 patients (24.0%) were improved less than 20%, and 22 (44%) were not improved or aggravated. Of the 3 patients who showed complete remission, 2 were from the age group 'under 5'. A total of 16 subjects were tested from this age group and this made up 18.8% of that group. The remaining 1 patient was from the age group '5 years or older'. A total of 34 subjects were tested from this group yielding a 2.9% remission rate. Among the 22 patients who showed no clinical improvements whatsoever, 6 belonged to the age group 'under 5' (37.5% of a total of 16 subjects tested in this group) and 16 belonged to the age group '5 or over' (47.1% of a total of 34 subjects tested in this age group).

By combination of IFN-γ therapy and diet therapy, another 14 patients (31.1%) showed complete remission and 14 (31.1%) showed improvements of more than 20%, 10 (22.2%) showed improvements of less than 20%, and 7 (15.6%) did not improve or were rather aggravated. In the control group that did not receive any treatment, no patient reached a complete remission, 2 (6.7%) improved more than 20%, 15

patients (50.0%) showed slight improvements of less than 20%, and 13 (43.3%) patients showed no improvements or were rather aggravated. Of the 14 patients who showed complete remission, 8 were from the age group 'under 5'. A total of 12 subjects were tested from this age group, yielding a 66.7% rate of remission for this group. The remaining 6 patients were from the age group '5 years or older'. A total of 33 subjects were tested from this group yielding an 18.2% remission rate. Of the 7 patients who showed no clinical improvements whatsoever, 0 belonged to the age group 'under 5' (0% of a total of 12 subjects tested in this group) and 7 belonged to the age group '5 or over' (21.2% of a total of 33 subjects tested in this age group).

An analysis of the distribution in the extent of improvements between the initial and the final clinical severity scores before and after treatment was performed (Fig. 4). The extent of clinical improvement by the elimination diet group was limited to a narrow distribution (Fig. 4b). Limited improvement but a high response rate was obtained using the elimination diet. The extent of clinical improvement by IFN-γ therapy was marked by a wide distribution (Fig. 4c).

The typical symptomatic fluctuation during IFN-γ therapy of AD (Fig. 5a) disappeared when the elimination diet was applied simultaneously (Fig. 5b). A positive food challege following a successful IFN-γ therapy combined with an elimination diet brought about abrupt aggravations of clinical severity. (Fig. 5c). During the IFN-γ therapy with diet elimination, a positive food challenge induced a symptomatic aggravation that was similar to the fluctuation seen during the IFN-γ therapy without elimination diet in AD (Fig. 5d).

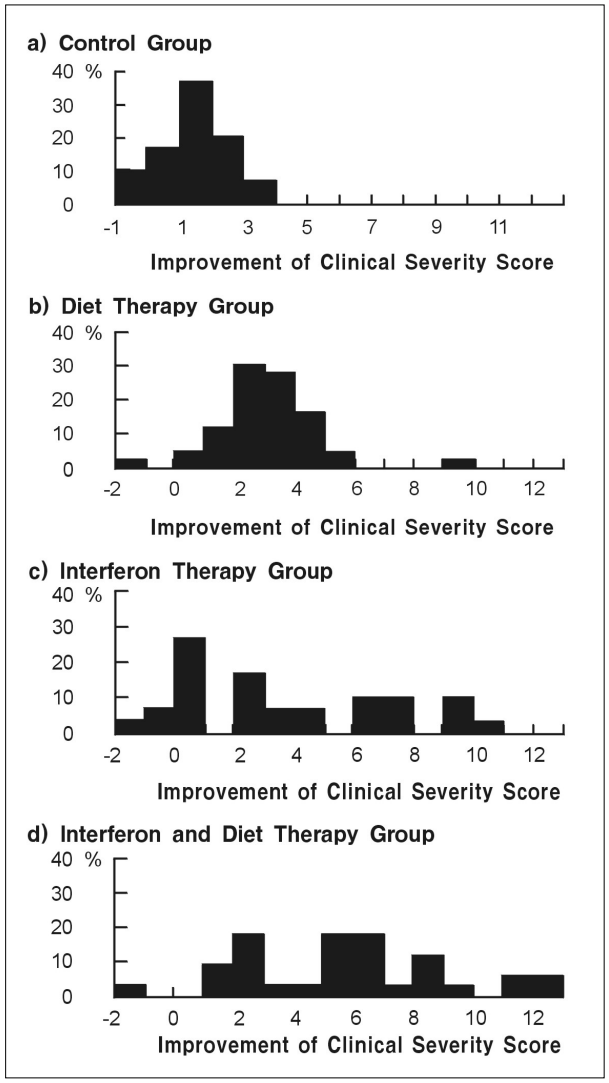

Fig. 4. The characteristics of clinical results by diet therapy, interferon (IFN)-γ therapy, and diet + IFN-γ therapy. Y axis is the percentage of patients included in each group.

Open food challenge test

Open food challenge tests were conducted on 316 (60.3%) 524 AD patients included in this study. The AD patients who showed a positive reaction to the challenge of at least one food totaled 77.8%. Open food challenge tests were conducted with a mean 2.8 type of food per patient (ranging from 1 to 10 foods). Among the 897 open food challenge tests in this study, a total of 558 tests (62.2%) showed positive responses of either newly developed or increased symptoms and/or signs such as pruritus (96.4%), erythema (92.5%), edema/papulation (76.2%), scaling/dryness changes (88.2%), and excoriation (54.5%). Only 120 cases (21.5%) of 558 positive tests showed immediate reaction within several hours. During the open food challenge, 37.4% showed obvious clinical manifestations in as early as 3 days and others took a maximum of 7 days. Only one patient showed exaggerated asthma and there was no systemic anaphylactic reaction observed during the open food challenges.

There was no significant relationship between the positive challenges to milk and beef or between egg and chicken as compared to those among other allergens (data not shown). The prevalence of food allergies by open food challenges in AD were as follows; chicken (65.9%), milk (65.3%), pork (64.8%), egg (61.9%), cod/catfish (48.0%), sesame (38.3%), wheat (34.6%), tuna (34.0%), beef (27.5%), bakers yeast (23.6%), mushroom (18.6%), mackerel (12.0%), soybean (10.5%), chocolate (9.6%) and potato (9.0%).

Results of past history, skin prick test, and specific IgE

The positive results of past-history taking, skin prick test, and specific IgE detection were variable and differed from one another (Table 1). The 6 most common foods to which patients had experienced allergies in the past were as follows, in order of appearance: chicken (23%), pork (21%), egg (16%), milk (12%), mackerel (9.2%), and tomato (8.8%). However, according to the skin prick test, the most frequent positive foods were as follows; tuna (68%), wheat (68%), shrimp (57%), mushroom (56%), milk (54%), and clam (52%). By specific IgE detection, the 6 most common positive foods were as follows: milk (64%), egg (58%), soybean (49%), beef (41%), pork (41%), and crab (35%).

In order to evaluate the usefulness of the skin prick test and specific IgE detection, statistical descriptions such as sensitivity, and specificity for chicken, beef, egg, and milk were analyzed (Table 4, a and b). In particular, food challenges with chicken showed a positive result rate (61.0%) although both the skin prick test and specific IgE detection were negative. On the other hand, food challenges with beef showed a high negative result rate (60.4%) despite the positive results of both the skin prick test and specific IgE detection (Table 4c).

Table 4. Statistical Description of Skin Prick Test and Specific IgE.

a)

SPT	n	Sensitiviity	Specificity
Chicken		31.7	87.1
Beef	60	87.9	18.5
Egg	258	17.4	66.7
Milk	199	43.9	70.1

b)

SIgE	n	Sensitiviity	Specificity
Chicken	185	10.6	9
Beef	60	24.2	70.4
Egg	258	12.3	81
Milk	199	22	80.6

c)

	*(-)/(-) → (+)	*(+)/(+) → (-)
Chicken	61.0% (75/123)	28.6% (18/63)
Beef	0 % (0/33)	70.4% (19/27)
Egg	24.1% (47/195)	19.4% (13/67)
Milk	45.5% (60/132)	12.9% (8/62)

a) Skin prick test (SPT). b) Specific IgE (sIgE). c) The results of food open challenge tests in cases of both negative and both positive results in skin prick test and specific IgE.
*SPT/sIgE → Results of food challenge tests.

DISCUSSION

The elimination diet effectively improved clinical severity scores in AD. Moreover, it improved the clinical results of IFN-γ therapy of AD (Fig. 1). Although allergists and dermatologists have different opinions concerning the prevalence and importance of food allergy in AD,[19] food hypersensitivity has been reported to play an important role in the pathogenesis of AD.[20] In this study, 58.1% of AD patients improved more than 20% in their clinical severity scores using the elimination diet. Elimination diet processes were suggested by EAACI 21, as well as other investigators,[22] with different response rates (38%[13], 52%[23], and 91%[24]). Interestingly, 77.8% of AD patients showed positive challenges to at least one food in this study. In other reports, 72% of AD patients showed food allergy,[25] and 38.7% were interpreted as having positive challenges.[26] Despite a positive challenge rate (77.8%), the clinical response rate to dietary manipulation was 58.1% in this study. These results suggested the other factors other than foods, might also be responsible for AD, although foods played an important role in AD.

In this study, the elimination diet was impor-

tant regardless of age. However, there were more patients who did not respond to diet elimination in the age 5 years or older group compared to the younger than 5 years group. Conversely, there were more patients who showed good response results to diet elimination among subjects in the younger than 5 years of age group than among subjects in the group aged 5 years or older. Food allergy might play an important role in adults.[27] However, diet elimination was more effective on AD patients under the age of 5 compared to those 5 years of age or older.

Total eosinophil counts decreased significantly by with the elimination diet as compared to those of the control group. From these results, it is suggested that avoidance of allergenic challenges may decrease the total eosinophil counts. These results may suggest a clue to solving the role of eosinophil in the pathogenesis of AD. However, the elimination diet did not change the serum IgE level.

The two characteristics of clinical response with the elimination diet (Fig. 4) were 1) better results in the mild status than in the severe status; and 2) a limited extent of improvement. IFN-γ therapy showed a marked clinical improvement but a low response rate. Although the response rate of IFN-γ therapy was lower than that of elimination diet, the degree of clinical improvement was better in the IFN-γ therapy as compared to an elimination diet (Fig. 4, b and c). Interestingly, by combining IFN-γ therapy and elimination diet, the extent of clinical improvement was markedly improved, with a simultaneous high response rate.

In our previous report,[9] a clinical fluctuation during the course of IFN-γ therapy in AD was noticed (Fig. 5a). In food-responsive AD patients who showed a positive food challenge test to at least one food, clinical fluctuations disappeared through the elimination diet during IFN-γ therapy (Fig. 5b). Interestingly, a similar clinical fluctuation in the clinical course reappeared as a result of positive food challenges after a successful IFN-γ therapy (Fig. 5c). Additionally, a positive food challenge during a successful IFN-γ therapy led to clinical fluctuations similar to the clinical pattern observed in IFN-γ therapy without elimination diet (Fig. 5d). From these results, food factors seemed to be responsible for the clinical fluctuation during the course of IFN-γ therapy. Consequently, an elimination diet may be essential for successful IFN-γ therapy in AD. Moreover, these phenomena were important findings which suggested that a food challenge test was possible during IFN-γ therapy in AD.

In many reports, an immediate reaction has been observed as the results of food challenge test.[19,27] Only 21.5% cases of the 558 positive challenge tests showed an immediate reaction in this study. The remains showed only delayed reactions due to the open food challenge test. During the open food challenge, 37.4% showed obvious clinical manifestation such as itching or skin manifestations even after even after 3 days and after a maximum 7 days. There remains a controversy concerning the existence of delayed reactions to foods. However, delayed reactions to foods were reported to be notable features.[28,29] It is recommended to observe patients for at least 10 days in order to decide the results of open food challenge tests.

The prevalence of 8 specific foods allergies that

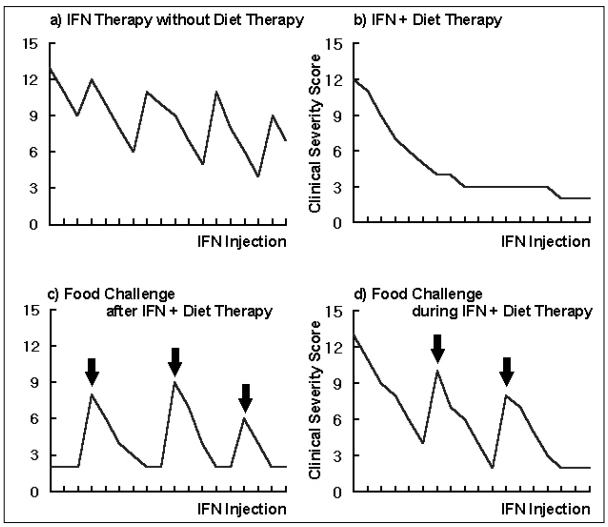

Fig. 5. A typical example concerning the effects of an elimination diet in interferon (IFN)-γ therapy in AD. a) The clinical course of IFN-γ therapy of food-responsive atopic dermatitis without elimination diet. b) The clinical course of IFN-γ plus elimination diet in food-responsive atopic dermatitis. c) The clinical course by food challenge after IFN-γ plus elimination diet in food-responsive atopic dermatitis. d) The clinical course by food challenge during IFN-γ plus elimination diet in food-responsive atopic dermatitis. Vertical black arrows indicate positive food challenges in figure 4c and 4d.

showed positive food challenge in more than 30% of AD patients enrolled in this study were chicken, milk, pork, egg, cod/catfish, sesame, wheat, and tuna. Egg, milk, peanut, and soy accounted for 87% of confirmed reactions.[25] Seven foods (milk, egg, peanut, soy, wheat, cod/catfish, cashew) were reported to account for 89% of the positive challenges.[26] The noticeably incriminated foods in this study were chicken, pork and sesame as major causative allergens for food allergy in AD in Korea. Chicken and pork were regarded as minor causative allergens in many other reports. The positive rate of oral cow milk challenges was 65.3% of total cow milk challenges in this study compared to 54% in a previous report.[30]

Skin prick tests and specific IgE detection are not helpful because of the high rates of false positive[31] and false negative report.[32] A combination of a skin prick test and specific IgE detection for the identification of food allergy was recommended by this study (Table 4). In spite of the high concordance rates for egg and milk by such an approach, those were low for chicken and beef (Table 4c). These low predictive of the skin prick test and identification of specific IgE might be explained by non-IgE mediated allergy mechanism.[22]

Conclusively, an elimination diet had therapeutic effects on IFN-γ therapy in AD. A food challenge test was possible during IFN-γ therapy. The elimination diet was more important for AD patients with an age less than 5. Foods may be important factors responsible for the clinical fluctuation during the IFN-γ therapy in AD. Therefore, an elimination diet may be essential for successful IFN-γ therapy in AD.

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