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A Probable Involvement of Rice Allergy in Severe Type of Atopic Dermatitis in Japan*

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1006 patients with typical and atypical lesions of atopic dermatitis (AD) were analysed statistically. The clinical severity was closely correlated to serum IgE values and RAST (radio-allergosorbent test) positivity. The frequency of RAST-positive antigens was significantly correlated with serum IgE values ($\gamma = 0.712$; $p < 0.01$). The analysis of multiple correlation between the clinical severity and each RAST score for mite, egg white and rice antigens suggested a strong contribution of rice allergy to the development of severe AD. 25 patients with severe AD and positive rice-RAST were treated by rice exclusion diet. The results were as follows: 9 cases remarkably responsive, 10 cases moderately responsive and 6 cases unresponsive. The rice-RAST titre decreased most remarkably in the 1st group. The wheat-RAST titre also decreased in the 1st, in spite of taking wheat foods every day, but increased in the 3rd. A probable role of rice allergy in severe AD in Japan is discussed.

Key words: Atopic dermatitis; Rice allergy; Multiple correlation between clinical severity and RAST; Statistical analysis; Elimination diet.

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Atopic dermatitis (AD) is a recurrent, itching, eczematous skin disease, which is inherently susceptible to disordered regulation of IgE- and T-cell-mediated hypersensitivity reactions and vascular responses (1). However, it has still not been demonstrated what plays the crucial role in the development or exacerbation of AD, in spite of all previous investigations. Inhalants such as mites, pollens and moulds and many kinds of foods have been suggested as a etiological antigens of AD, due to the presence of IgE antibodies to these antigens in the sera of AD patients (2, 3). Among the food antigens, egg white, milk and soy bean have been well studied, as many pediatricians have long insisted that they are the three major allergens causing infantile AD, but cereal allergens such as rice and wheat have not received the same attention. In this paper we present data suggesting a probable involvement of rice allergy in the severe type of AD.

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MATERIAL AND METHODS

Subjects and diagnostic criteria for AD

One thousand and six patients with typical and atypical lesions of AD were included in this study. Typical infant eczema on the face and head (infant type); eczematous eruptions on flexural areas, such as cubital fossa, poplitea and neck (flexural type); brown hard nodular papules anywhere on the body (prurigo type); and follicular papules, often with pityriatic scales on the trunk (dry skin type), were all considered typical lesions of AD, as described by Uehara & Ofuji (4). Other lesions, believed to be associated with AD, were regarded as atypical lesions (4, 5).

Definite AD (d AD) was diagnosed by presence of four items: 1) itching, 2) chronic course of more than one year, 3) atopic history, and 4) typical lesions of AD. The other cases were diagnosed as indefinite AD: 3 items positive, 2 items positive, and 1 item positive (3 + iAD, 2 + iAD and 1 + iAD).

Grading of clinical severity

The clinical severity of the AD lesions was graded as of (I) mild, (II) moderate, or (III) severe type, according to the expansion of the lesions, responsiveness to therapy, frequency of relapse, and the clinical course, as follows. (I) mild: the lesions are relatively limited or disparately scattered, readily responsive to therapy and not so often relapsing, and then the course is short; (II) moderate: the lesions are expanded or occasionally limited, relatively responsive to therapy, but often relapsing and then the course is chronic; (III) severe: the lesions are expanded or occasionally limited, refractory to therapy and then the course is chronic and very protracted.

Measurement of specific IgE antibodies

Serum IgE antibodies specific to many inhalant and food antigens were determined with the Phadebas RAST (radio allergosorbent test) kit (6). The results were expressed in PRU/ml (Phadebas RAST Units/ml) or with the RAST scoring system (score 0: ≦0.34 PRU/ml, score 1: 0.35 ~ 0.69, score 2: 0.7 ~ 3.4, score 3: 3.5 ~ 17.4, and score 4: ≧17.5 PRU/ml). A result exceeding 0.34 PRU/ml (score ≧1) was considered positive.

Absorption with antigen disc on the RAST titre for soy bean, rice and wheat antigens

The five serum samples which were RAST positive to each antigen of soy bean, rice and wheat, were absorbed by ¼ to 2 discs of these antigens and assayed for the measurement of IgE antibodies specific to them by the RAST method, in order to examine a cross-reactivity of IgE antibody among the cereal antigens. The effect by absorption with antigen disc was expressed as a percentage of the post-absorption titre of RAST to the original titre.

RESULTS

Evaluation of diagnostic criteria

The positive percentages of typical lesions of AD, chronic course and atopic history decreased step by step with de-

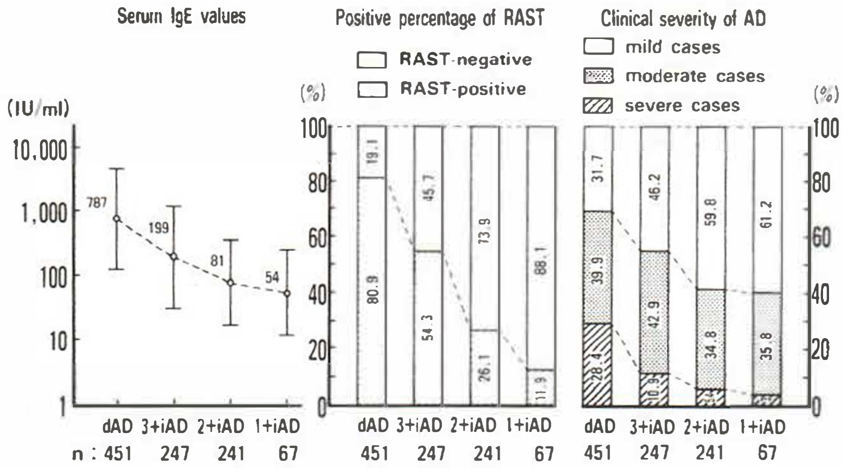


Fig. 1. Serum IgE values, positive percentage of RAST and clinical severity in the subgroups graded by the diagnostic criteria for AD.

creases in the grading of criteria for AD, whereas that of itching registered scarcely any change. Especially the frequency of typical lesions decreased remarkably and was only 6.6% in the patients with 2 + iAD. Moreover, the serum IgE values, the positive percentage of RAST for more than one antigen, and clinical severity all decreased step by step with decreases in grading of criteria for AD, as shown in Fig. 1.

Relationship between clinical severity and serum IgE and RAST

The serum IgE values increased significantly ($p < 0.01$) as clinical severity worsened. The RAST positivity for more than one antigen also increased parallel with clinical severity. We then examined correlations between serum IgE values and frequency of RAST-positive antigens. The latter was calculated from the following formula: 100× (number of positive antigens/number of antigens tested in the RAST). The results revealed a very high correlation coefficient ($\gamma = 0.712$; $n = 948$, $p < 0.01$), between serum IgE values and frequency of RAST-positive antigens.

Table I. *Correlation coefficients among RAST scores (0 ~ 4) for several antigens.*

Antigens used for RAST — Case number tested (upper right); Correlation coefficient (lower left)

D.F.	894	951	932	532	373	213
0.9248	HD	917	903	508	349	203
0.2365	0.2428	Egg White	963	534	372	214
0.2197	0.2541	**0.6437**	Milk	529	365	207
0.3359	0.3469	0.4150	0.3400	Soy Bean	308	181
0.5239	0.5520	0.4577	0.3976	**0.6463**	Rice	188
0.4079	0.4396	0.4370	0.3954	**0.6721**	**0.7830**	Wheat

Bold square indicates correlation coefficient of over 0.6
($p < 0.01$ in all of the correlation coefficient)

Correlations among RAST scores for several antigens

Since the correlation between frequency of RAST-positive antigens and serum IgE values was very high, the RAST scores for several antigens were presumed to be mutually correlated. In fact, when we calculated the correlation coefficient among the RAST scores for several antigens, there turned out to be a very close correlationship between DF (*Dermatphagoides farinae;* mite antigen) and HD (house dust), and a relatively close correlationship between egg white and milk, soy bean and rice, rice and wheat, and wheat and soy bean, respectively, as shown in Table I.

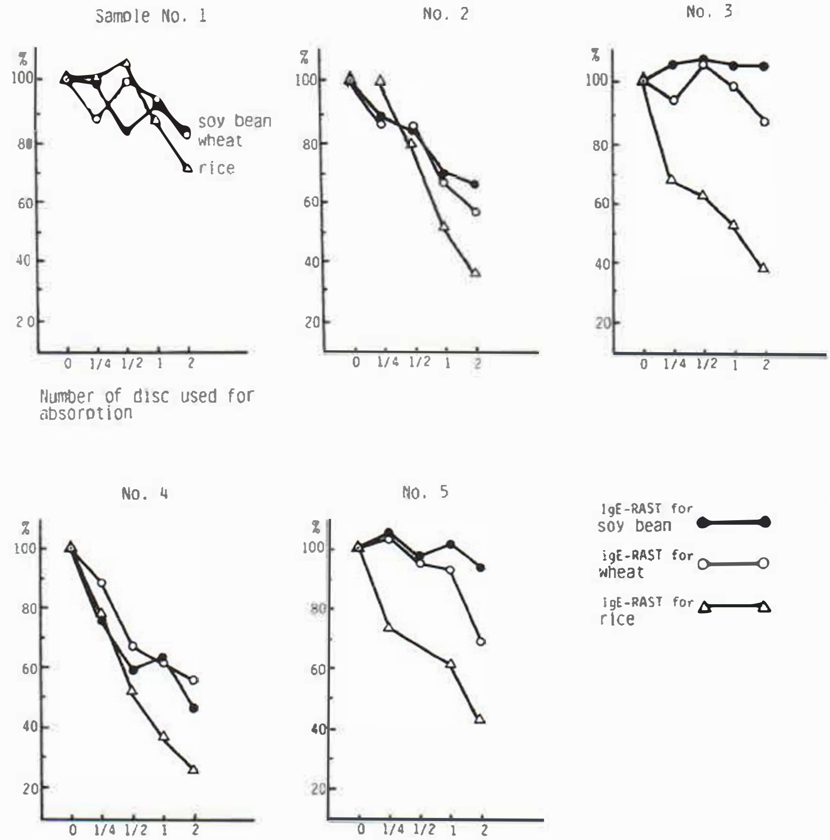
Fig. 2 shows the effect of absorption with rice disc on RAST titre for soy bean, rice, and wheat antigens. The RAST titre for these cereal antigens was reduced dose-dependently by absorption with rice disc in some sera (see nos. 2 and 4 in Fig. 2). The RAST titre for these cereals was also reduced by absorption with wheat and soy bean disc in some sera (data was not shown).

Correlations between clinical severity and RAST scores for DF, egg white, and rice antigens

Since a correlationship was observed between DF and HD, between egg white and milk, and also among soy bean, rice and wheat, we selected three antigens of DF, egg white and rice as the representative antigens, and first examined the age distribution of RAST positivity for these antigens in 692 patients with typical lesions of AD. The results revealed that RAST positivity for egg white was very high even in already on 0–1-year-olds, decreasing after 2 years of age, while positivity for DF increased rapidly after 1 year of age, subsequently forming a plateau (60–80%), while that for rice reached the level of 30–50% after 2 years of age, as seen in Fig. 3.

The RAST positivity for rice was lower than that for DF at all ages, but appeared to be better correlated with the clinical severity than that for DF and egg white (data not shown). We then calculated multiple correlations between clinical severity (I to III) and RAST scores (0 to 4) for these three antigens in the 184 patients with dAD. The standard partial regression coefficient of the rice-RAST scores for clinical severity was the highest in each age group as well as for all the patients, as shown in Table II.

Fig. 2. Effect of absorption with rice disc on the RAST titre for soy bean, rice and wheat antigens.



Effect by exclusion of rice from diet on clinical course of AD and RAST titre for rice and wheat

From the above-mentioned results, we treated 25 patients with severe-type of AD by excluding rice from the diet for several months (1 ~ 8 months). Mean age, mean percentage of blood eosinophils, mean serum-IgE value, and geometric mean RAST titre for rice and wheat in these patients were: age 24.7, 8.5%, 4677 IU/ml, 2.44 PRU/ml and 1.50 PRU/ml, respectively.

The results were as follows: 1) 9 cases (36%) remarkably responsive, 2) 10 cases (40%) moderately responsive, and 3) the other 6 cases (24%) unresponsive (no effect, or exacerbation). The geometric mean of rice-RAST titre decreased several months (mean: 5.5 months) after treatment by exclusion of rice from the diet in each group; its decrease in the 1st group was the most remarkable. However, an increase in rice-RAST titre was found in some cases in the 2nd and 3rd groups, accompanied by an increase in wheat-RAST titre (data not shown). Interestingly, the wheat-RAST titre also decreased several months after commencing the rice elimination diet in most cases (8/9) in the 1st group, in spite of taking wheat foods every day, but increased in half of the cases (5/10) in the 2nd and in all the cases (6/6) in the 3rd group. Furthermore, the AD lesions in some cases in the 3rd group were aparently aggravated by the rice elimination diet, but were ultimately improved by adding a wheat elimination diet to it.

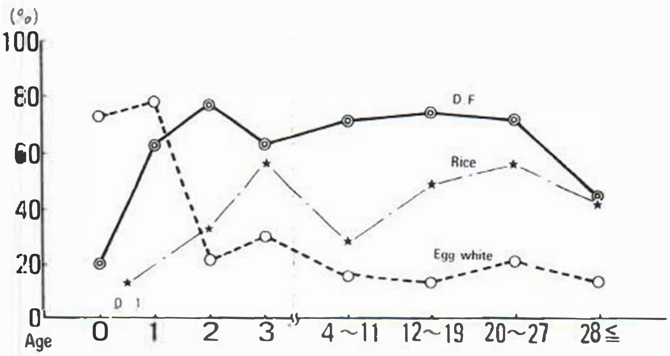


Fig. 3. Age distribution of RAST positivity for DF, egg white and rice antigens in the patients with typical lesions of AD.

Table II. *Multiple correlations between the clinical severity (I ~ III) and RAST scores (0 ~ 4) for DF, egg white and rice antigens in the patients with definite AD.*

		Standard partial regression coefficient of the RAST scores for the clinical severity				
		0~9y (n=34)	10~19y (n=84)	20~29y (n=41)	30y~ (n=25)	all patients (n=184)
Antigens tested for RAST	D.F.	0.0124	0.1211	0.0272	0.1443	0.1209
	Egg white	0.0599	0.1039	0.0072	0.1089	0.0336
	Rice	0.6816	0.3822	0.5102	0.3955	0.5171
Multiple correlation coefficient		0.6116	0.4724	0.6320	0.5223	0.5739

n Number of patients analysed

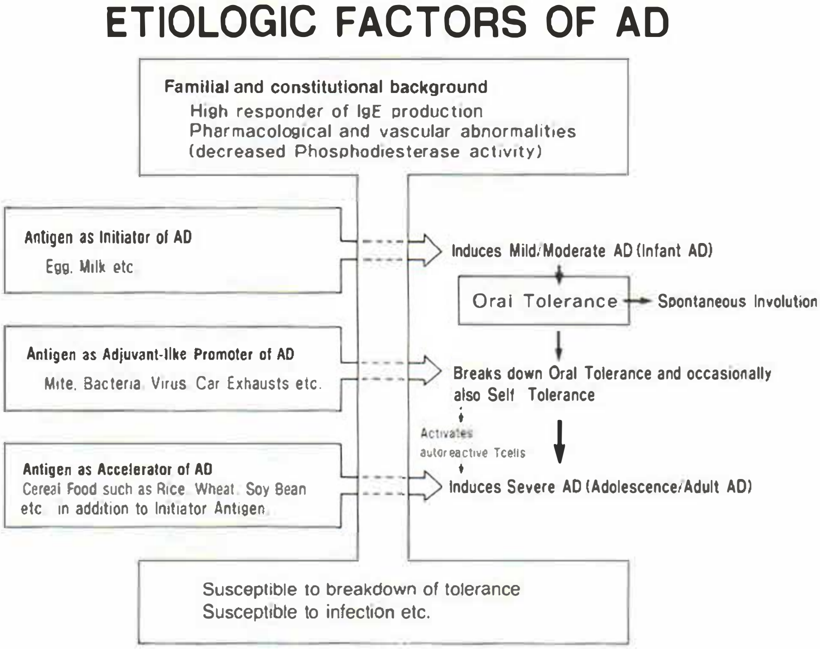


Fig. 4. Hypothetical etiologic factors in AD.

DISCUSSION

Analysis of the four items which we proposed as diagnostic criteria for AD indicated that the typical lesions appeared to be the most specific item for a diagnosis of dAD. The serum-IgE values, RAST positivity for more than one antigen, and clinical severity all increased with an increase in the grading of AD criteria. These results suggested that these criteria might be useful for grading the diagnosis of AD. Thus 3 + iAD and 2 + iAD may be termed as probable AD and possible AD, respectively. The statistical analysis in this study revealed that the clinical severity of AD was closely related with serum-IgE values and RAST positivity for more than one antigen. The frequency of RAST-positive antigens was revealed to be significantly correlated with the serum IgE values ($\gamma = 0.712$, $p < 0.01$).

The statistical analysis also revealed a close correlation between each RAST score of DF and HD, egg white and milk, soy bean and rice, rice and wheat, and wheat and soy bean. This correlation among RAST scores for cereal antigens such as soy bean, rice and wheat was suggested to reflect that these antigens shared some antigenic epitopes for IgE antibodies with one another from the absorption experiment.

The analysis of multiple correlation between the clinical severity and each RAST score for DF, egg white and rice antigens suggested a strong contribution of rice allergy to the development of severe AD. However, the multiple correlation coefficient was not so high either in each age group or in all the patients. These results mean that clinical severity cannot be explained even by the sum of the rice, egg white and DF-RAST scores, which are interpreted as indicators of the IgE-mediated hypersensitivity to rice, egg white and DF. Probably other factors are presumed to be involved in the development of severe AD.

The effect of the rice elimination diet on the clinical course of AD and the rice- and wheat-RAST titre may give some suggestion as to what one of another factors might be. Namely, a decrease in the wheat-RAST titre by eliminating rice from the diet in most cases in the 1st group suggests that rice antigen may affect the production of IgE-antibodies specific not only to rice but also to wheat as an inducer antigen, at least in these cases. By contrast, a paradoxical increase in the rice-RAST titre by excluding rice from the diet in some cases in the 2nd or 3rd group, with an increase in wheat-RAST titre, suggests that wheat antigen may also affect the production of IgE-antibodies specific to rice as an inducer antigen in these cases. Consequently, epitopes of these antigens having a relation to the development or exacerbation of AD are presumed to fall into two groups. One group is composed of hapten-like epitopes, which react with IgE-antibodies, and the other consists of carrier-like epitopes which induce the production of IgE-antibodies, probably by the induction of helper T (Th; Th_2?) cells (7, 8). The Th (Th_1?) cells induced by the carrier-like epitopes may also cause delayed hypersensitivity reactions, which are believed to be closely associated with the major part of eczematous tissue reactions in AD (8). Therefore, it is presumed that the carrier epitopes of rice antigen inducing the production of IgE-antibodies to not only rice but also to other cereal antigens may play an important role in the development of severe AD in Japan, where rice foods are the most popular and staple cereals. However, it has still not been demonstrated how oral tolerance to cereal antigens, which is believed to be usually induced, is broken down in the severe type of AD in patients with food allergy (9). We wonder if these patients are inherently susceptible to the breakdown of oral tolerance, and also if many kinds of allergens such as mites, bacteria virus, motor vehicle exhausts, metals and so on act as adjuvant-like promoters or immunomodulators, resulting in the breakdown of oral tolerance. Recently, Taylor et al. (10) have reported that autoreactive T cell-mediated autoimmune responses to epidermis may play a role in the pathogenesis of AD. Fig. 4 is a schematic illustration of hypothetical etiologic factors in AD as we imagined them from the discussion above. From this view the investigations into the immunology of rice antigen, its distribution within the body after ingestion, T cell responsiveness to it and oral tolerance to it, are still in progress.

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