

IgE antibodies to *Pityrosporum orbiculare* and *Staphylococcus aureus* in patients with very high serum total IgE

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Summary

Serum IgE antibodies were detected with the radioallergosorbent test (RAST) to a panel of allergens which included *Pityrosporum orbiculare*, *Candida albicans*, *Trichophyton rubrum*, *Cladosporium herbarum*, *Staphylococcus aureus*, animal dander, deciduous tree pollens, grass pollens and foods in 81 consecutive patients with total IgE ≥ 3000 kU/l. Data on atopic and infectious disease characteristics were collected by a questionnaire. IgE antibody concentrations to *P. orbiculare* were significantly higher than to the other fungi and of the same magnitude as those to animal danders and pollens. High levels of *P. orbiculare* IgE antibodies were associated with current eczema, especially when it was the only atopic manifestation and demanding specialist care. IgE antibodies to *P. orbiculare* had the best explanatory value for current eczema in logistic regression analysis. Head-neck-face dermatitis was also associated with high levels of specific IgE to the yeast. IgE antibodies to *S. aureus* were detected in few patients and at low concentrations. Six patients had a history of systemic staphylococcal infections and presented a clinical picture, which was very similar to the hyperimmunoglobulinaemia E syndrome. Among the six were the two cases with the highest levels of IgE antibodies to *S. aureus*. The demonstration of high levels of IgE antibodies to *P. orbiculare*, which is a major part of human normal skin microflora, suggests that allergy to this yeast plays an important pathogenic role in eczema.

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Introduction

In a previous study of atopic children [1] we found a strong association between fungal sensitization and eczema. In an extension of that study IgE antibodies to the lipophilic yeast *Pityrosporum orbiculare* were found preferentially in the sera of children with atopic sensitization to inhalant moulds, and IgE antibodies to *P. orbiculare* had the best explanatory value for atopic eczema [2]. Since this yeast constitutes a major proportion of the saprophytic microflora of human skin [3,4], allergy to *P. orbiculare* may be important in the pathogenesis of

atopic dermatitis. This interpretation also lends support from others [5,6,7]. In the hyper-IgE (Buckley) syndrome the clinical picture is dominated by a severe dermatitis and infection proneness [8,9]. IgE antibodies to *Staphylococcus aureus* and *Candida albicans* have been implicated in the pathogenesis of the dermatitis of the syndrome [9]. IgE antibodies to *C. albicans* and *P. orbiculare* are possibly cross-reactive [2] and *P. orbiculare* is the yeast of the two which colonizes the skin to the greatest extent. Therefore allergy to *P. orbiculare* may be an important pathogenic factor not only in atopic eczema but also in the hyper-IgE syndrome.

In the present study we have focused on clinical features of the atopic diseases, eczema in particular, but

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also of the hyper-IgE syndrome in patients with high levels of serum IgE and attempted to relate the disease traits to levels of IgE antibodies to a panel of common allergens which also included *P. orbiculare*, *C. albicans*, *Trichophyton rubrum* and *S. aureus*.

Patients and methods

Patients

Consecutive cases of patients with serum IgE ≥ 3000 IU/ml, and serum available in the bank of the Allergy Diagnosis Laboratory of the Department of Clinical Immunology, Karolinska Hospital were studied. The sera had been sent for routine analyses, which included determination of total IgE, from September 1987 to July 1988. The laboratory mainly covers the northern and western parts of Stockholm and patients attending a wide spectrum of clinics of different specialists as well as general practitioners. A questionnaire, which included a formal request for permission to use their available serum for analysis was submitted to the patients. Such permission was obtained from 81 of 90 patients, who also completed the questionnaires and were finally included in the study. They were 35 males and 46 females with ages ranging from 7 to 71 years (median 29).

Questions for current and previous allergic diseases; asthma, allergic rhino-conjunctivitis, eczema and food allergy were posed in the questionnaires. Questions which referred to the severity of asthma such as hospital care and need of medication were also included. The age of onset of eczema, its seasonal variations, need for hospital care and whether the patient consulted a specialist in dermatology were recorded. Special notice was paid to the distribution of the eczematous lesions on the body surface. A series of questions which referred to infection proneness were also asked. The study was approved by the ethical committee of the Karolinska Institute.

Analyses in vitro

Total IgE was analysed with IgE-RIA (Pharmacia AB, Uppsala, Sweden) following the recommendations of the manufacturer. IgE antibodies were analysed by the radioallergosorbent test (RAST) [10,11] to *P. orbiculare*, *C. albicans*, *T. rubrum*, *C. herbarum*, *S. aureus* and mixed discs of deciduous tree pollens, grasses, animal epithelia and foods, respectively. Commercially available reagents (Pharmacia AB) were used except for the *P. orbiculare* and *T. rubrum* discs. The preparation of the *P. orbiculare* discs have previously been described in detail [2,12] and the *T. rubrum* discs were prepared accordingly using a *T. rubrum* extract [13] kindly provided by Dr L. V. von Stedingk, Central Microbiological Laboratory, Stockholm.

With few exceptions analyses were performed in duplicate. The results were related to a reference serum and expressed in Phadebas RAST units/ml (PRU/ml). Taking possible non-specific binding of IgE into account, only antibody levels ≥ 0.7 , i.e. above RAST class 1, were considered specific with the exception of the *S. aureus* and the food discs. For *S. aureus* binding below that of the 0.35 PRU/ml reference was found even at total IgE of 20000 kU/l, thus also levels corresponding to RAST class 1 were considered specific with this antigen. The food allergen discs gave obvious non-specific binding up to RAST-class 2, when only levels ≥ 3.5 PRU/ml were accepted. Serum was insufficient for RAST analyses to *T. rubrum* in seven and to foods in eight patients, respectively.

Statistical analyses

The Wilcoxon matched-pairs signed ranks test was used in the comparison of IgE antibody levels to the different allergens under study and the Mann-Whitney test for comparison of IgE antibody levels of different subgroups of patients. The Spearman rank test was used for correlation analyses. One multivariate technique, Cox's linear logistic regression analysis [14] was applied (BMDPLR-Stepwise logistic regression package, BMDP Statistical Software Inc., Los Angeles, California, U.S.A.) including age in the analyses. Using this model the probability (P) to contract the disease in question can for each patient be expressed as

$$P = \frac{e^y}{1 + e^y}$$

where $y = a + b_1x_1 + b_2x_2 + \dots + b_nx_n$

Results

Serum IgE antibodies to *P. orbiculare* were detected by the RAST tests in most of the patients and a majority of the sera held IgE antibodies in RAST classes 3 and 4 (Fig. 1). *P. orbiculare* IgE antibody concentrations were of the same magnitude as those to well-known inhalant allergens such as animal epithelia, grass and tree pollens and significantly higher than those detected to the other three fungal species, *S. aureus* and foods ($P < 0.001$). Females had significantly higher *P. orbiculare* IgE antibody levels than males ($P < 0.02$) and such IgE antibodies were more frequently detected in patients above 20 years of age (56/65) than below. *P. orbiculare* IgE antibody concentrations correlated weakly with IgE antibody levels to *C. albicans* ($r = 0.39$, $P < 0.01$), but not to any of the other allergens. *T. rubrum* IgE antibodies were detected approximately in one-third of the cases. The IgE antibody levels

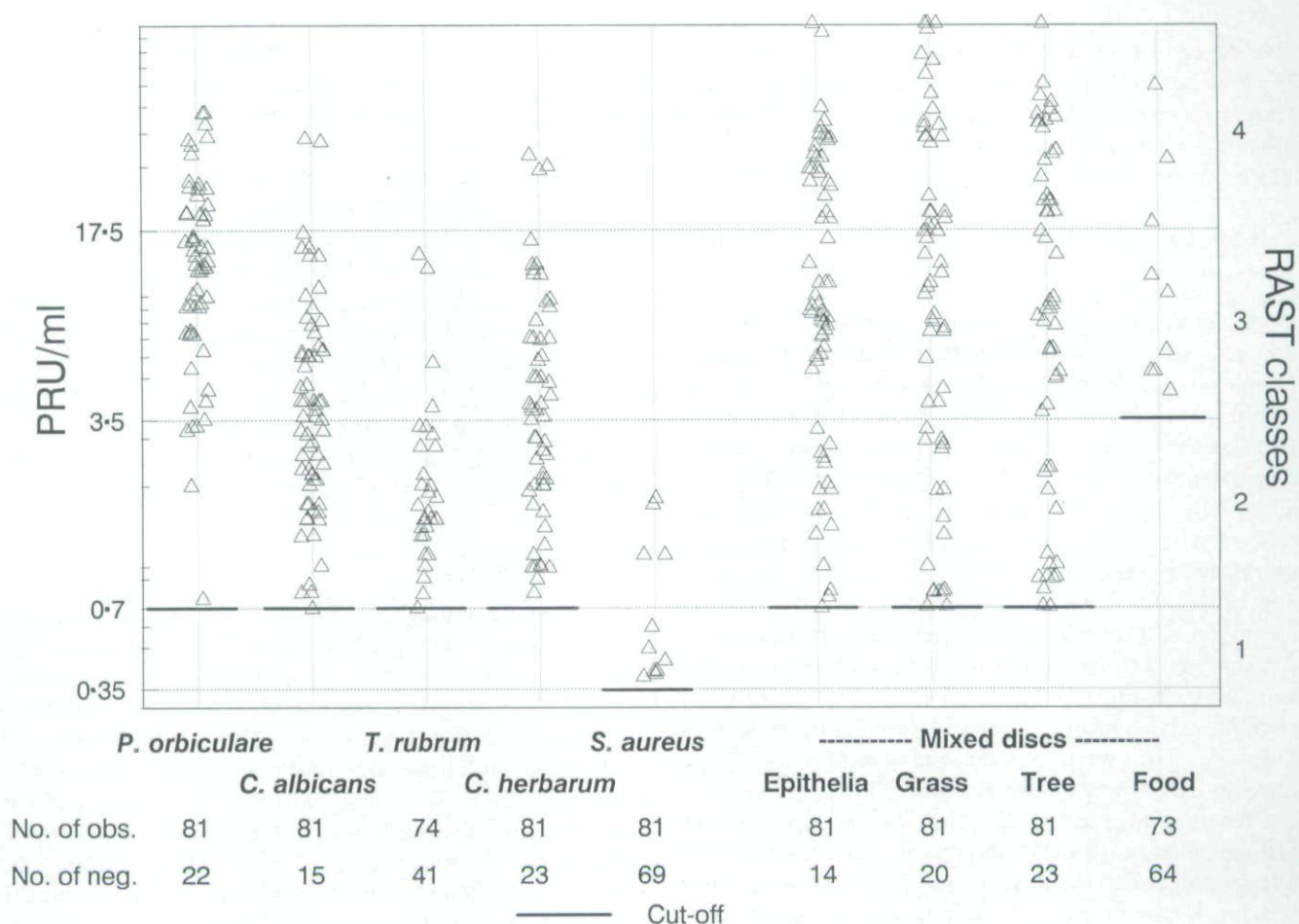


Fig. 1. IgE antibody levels as measured by RAST to *Pityrosporum orbiculare*, *Candida albicans*, *Trichophyton rubrum*, *Cladosporium herbarum*, *Staphylococcus aureus* and to the mixed discs of animal epithelia (epithelia), grass pollens (grasses), deciduous tree pollens (tree) and common food allergens (food).

Table 1. Median IgE antibody levels (PRU/ml) to *P. orbiculare* and other allergens in relation to atopic diseases. Ranges for IgE antibodies to *P. orbiculare* within parenthesis. (No. = number of patients, PO = *P. orbiculare*, CA = *C. albicans*, TR = *T. rubrum*, CH = *C. herbarum*, SA = *S. aureus*, Ex = animal epithelia, Gx = grass pollens, Tx = tree pollens, Fx = foods.)

	n	PO	CA	TR	CH	SA	Ex	Gx	Tx	Fx	IgE
Asthma	1	0	2.6	0	0	0	35	0	0	0	4600
Asthma + eczema	3	9.3 (0.76-16)	6.0	1.1	6.9	0	9.2	17	33	0	4600
Asthma + rhinitis	6	0 (0-7.2)	0.65	0	0	0	2.2	5.8	5.8	0	4400
Asthma + rhinitis + eczema	23	13 (0-47)	4.1	1.1	2.7	0	20	11	5.2	0	6900
Eczema + rhinitis	26	11 (0-39)	3.0	0	1.6	0	5.9	7.3	5.6	0	5800
Eczema	8	18 (3.3-33)	6.2	1.4	3.1	0	23	2.5	4.8	0	7700
Rhinitis	8	0 (0-15)	0.4	0	0	0	1.8	0.8	1.2	0	5000
None	6	0 (0-20)	0.75	0	0	0	0	0.4	0.45	0	3700

Table 2. Median IgE antibody levels (PRU/ml) in relation to some patient characteristics (y=yes, n=no). Other abbreviations as in Table 1.

		<i>n</i>	PO	CA	TR	CH	SA	Ex	Gx	Tx	Fx	IgE
Dermatology specialist	Y	38	14	4.0	1.4	2.4	0	11	12	8.6	0	6500
	N	22	7.8	3.0	0	1.8	0	7.1	4.9	3.8	0	5000
	<i>P</i>		<0.05	n.s.	<0.05	n.s.	n.s.	n.s.	<0.1	n.s.	<0.1	n.s.
Hospitalized for eczema	Y	28	14	3.9	1.5	3.2	0	9.2	9.2	7.1	0	6800
	N	31	9.4	3.3	0	1.6	0	11	7.9	5.2	0	5800
	<i>P</i>		n.s.	n.s.	<0.01	<0.1	<0.05	n.s.	n.s.	n.s.	<0.1	n.s.
Head-neck-face dermatitis	Y	11	14	4.1	0.8	2.7	0	10	14	8.4	0	7300
	N	36	6.3	2.0	0	1.0	0	7.1	1.5	0.9	0	4500
	<i>P</i>		<0.05	<0.01	n.s.	<0.1	n.s.	n.s.	<0.05	<0.1	n.s.	n.s.
Coarse facial skin features	Y	20	13	3.4	1.5	2.9	0	9.3	14	8.6	0	7100
	N	39	13	4.1	0.5	2.3	0	9.1	4.0	6.3	0	5800
	<i>P</i>		n.s.	n.s.	<0.05	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

against staphylococcal antigens were low in only in four patients of RAST class 2 and the highest detected level was only 1.8 PRU/ml.

Current asthma, rhinitis and eczema were related to the IgE antibodies to the different allergens (Table 1). Patients with atopic eczema had significantly higher IgE antibody concentrations to the four fungi than those without eczema (*P. orbiculare*, $P < 0.00001$; *C. albicans*, $P < 0.001$; *C. herbarum*, $P < 0.001$ and *T. rubrum*, $P < 0.01$). No significant differences of IgE antibodies to other allergens or of total IgE were found between these patient groups. The highest median IgE antibody levels to *P. orbiculare*, *C. albicans*, and *T. rubrum* were found in patients whose only acknowledged current atopic disease was eczema. Four of 21 subjects had no current eczema but exhibited significant IgE antibody levels to *P. orbiculare* (6.3–20 PRU/ml). All these cases had previously suffered from the disease.

With the multivariate approach IgE antibodies to *P. orbiculare* (po) had the very best explanatory value for current eczema ($y = -0.44 + 0.21 \cdot \text{po}$, $P < 0.001$). IgE antibodies to animal epithelia (ex) had the best explanatory value for asthma ($y = -0.95 + 0.035 \cdot \text{ex}$, $P < 0.05$), age ($P < 0.05$) and IgE antibodies to grass pollen allergens (gx) ($P < 0.1$) for rhinitis ($y = 2.35 + 0.035 \cdot \text{gx} - 0.046 \cdot \text{age}$). Perceived food allergy was best explained by IgE antibodies to *C. albicans* (ca) ($P < 0.01$), foods (fx) ($P < 0.05$) and age ($P < 0.05$) ($y = 0.85 + 8.79 \cdot \text{fx} + 0.18 \cdot \text{ca} - 0.052 \cdot \text{age}$). IgE antibody levels to *P. orbiculare* reached higher levels in patients with current eczema compared to those who had recovered from lesions

($P < 0.01$). Higher IgE antibody levels to fungi were also detected in patients with indications of severe disease, i.e. those who had consulted a specialist in dermatology and those who had been admitted to hospital for eczema, compared to those who had not (Table 2). IgE antibodies to *S. aureus* were also more common with severe disease. Cases with head-neck-face dermatitis had higher levels of IgE antibodies to the two yeasts than had patients without that particular distribution of the lesions. On the other hand coarse facial skin features paralleled *T. rubrum* rather than yeast IgE antibodies. IgE antibody levels to animal epithelia were unrelated to the aforementioned clinical features of eczema. Early versus late onset of eczema had no obvious relationship to any kind of RAST-positivity and this was also true for summer-time recovery or not.

Half of the patients with current eczema had received systemic antibiotic therapy for infected eczema. Their profile of sensitization did not differ from those who had not received such treatment; this was true also for patients who had a history of skin abscesses compared to those who had not. Six eczematous patients acknowledged systemic staphylococcal infections requiring hospitalization. Their pattern of IgE antibodies was not different from that of the other patients. However, two of them exhibited the highest values of IgE antibodies to *S. aureus*, 1.7 and 1.8 PRU/ml, respectively.

Discussion

The present findings of *P. orbiculare* IgE antibody levels as high as those to common inhalant allergens are highly

suggestive of an important role for *P. orbiculare* allergy in the pathogenesis of atopic diseases, eczema in particular. It is conceivable that other opportunistic or pathogenic fungi, in this study *C. albicans* and *T. rubrum*, are also of importance.

In orthodox allergology the demonstration of disease symptoms with application of the allergen in the chock organ, i.e. positive provocation test, is required as a proof of the clinical relevance of skin test and *in vitro* test results. However, in the case of *P. orbiculare* the allergen is already present on the skin [3], and it appears just as appropriate to demonstrate recovery from disease using fungicidal. Ketoconazole has been effective in a placebo-controlled study of *P. orbiculare* skin test positive subjects [15]. A management of the eczematous patient, which may include the establishment of *P. orbiculare* allergy and thereafter antifungal treatment, is indicated. The area, however, requires further penetration, e.g. of the possible effect upon eczematous lesions of prophylactic topical treatment with fungicidal that are free of side-effects.

The special inclusion criteria of the present study favoured patients with serious, combined atopic diseases in which the eczema obviously was of notable severity in many cases. The patients in fact appear very similar to those in a recent study of cases admitted for treatment of atopic eczema [16], who exhibited high IgE antibody concentrations to inhalants and foods. Allergy to *P. orbiculare* and other fungi may explain some of the clinical aspects of that study, e.g. the late onset severe eczema as well as the redevelopment of eczema in early adult life. These are features which could possibly be induced by the increasing colonization by *P. orbiculare* of the skin at puberty [4]. Our findings also support those of others with regard to the distribution of the eczema in *P. orbiculare* allergy [5,15].

Positive immediate skin test reactivity to trichophytin is known to be associated with *T. rubrum* infection, particularly chronic dermatophytosis [13,17–19]. In patients and families with chronic *T. rubrum* infections there is a high incidence of atopic disease [20] and children with an atopic background exhibit an increased risk to contract tinea pedis [21]. IgE antibodies to *T. rubrum* were prevalent also among the patients of this study most of whom manifested multiple fungal sensitizations. Although some inter-fungal crossreactivity may partly explain the presence of IgE antibodies to *T. rubrum*, atopic sensitization to dermatophytes may be of importance in the pathogenesis of severe eczema in certain patients and deserves further studies.

The intriguing relationship between sensitization to inhalant moulds and eczema was described by Kesten and Rajka some time ago [22,23]. In our previous study of children [2] there was a clearcut association between

atopic sensitization to inhalant moulds and *P. orbiculare*. In both studies IgE antibody levels to *P. orbiculare* correlated only to *C. albicans* indicating possible cross-reactivity of IgE antibodies. The qualitative association on the other hand between immune responses within the vastness of fungal antigens is likely to be due to immune response genes acting at the T-cell level. In our clinical practice we have observed that parents of children with *Cladosporium* asthma may suffer from atopic eczema with the peculiar head-neck distribution and a previously undiagnosed sensitization to *P. orbiculare*, an observation suggestive of a hereditary link.

In the present series of patients *S. aureus* IgE antibodies were sparse and only low levels were detected. Yet, clinical correlates were found in that the two patients with the highest levels of staphylococcal IgE had a history of systemic staphylococcal infection. These patients' clinical presentations were less severe but similar to most published cases with the hyperimmunoglobulinaemia E syndrome. This indicates a link between severe eczema with atopic allergy to fungi including *P. orbiculare* and *C. albicans* and the hyperimmunoglobulinaemia E syndrome and that the syndrome should not be seen as a separate disease entity. Allergy to yeasts, *P. orbiculare* in particular, may be an important factor in the pathogenesis of the eczema of this patient group as well as in many other cases of eczema, especially when severe.

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