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Occurrence and Clinical Features of Sensitization to *Pityrosporum orbiculare* and Other Allergens in Children with Atopic Dermatitis

LOUISE LINDGREN[1], CARL-FREDRIK WAHLGREN[2], S. GUNNAR O. JOHANSSON[3], INGRID WIKLUND[1] and S. LENNART NORDVALL[1,3]

[1]*Department of Pediatrics, St. Göran's Childrens's Hospital, Karolinska Institute, and Departments of* [2]*Dermatology and* [3]*Clinical Immunology, Karolinska Hospital, Karolinska Institute, Stockholm, Sweden*

One hundred and nineteen consecutive cases of children with atopic dermatitis aged 4–16 years (73 girls) from a pediatric dermatology outpatient clinic were included in a study of atopic sensitization. Structured interviews and clinical investigations were performed. IgE antibodies to common inhalant allergens, *Pityrosporum orbiculare, Candida albicans, Tricophyton rubrum* and *Staphylococcus aureus* were detected. Specific IgE antibodies frequently occurred to pollens, animal epithelia, *C. albicans,* house dust mites and moulds, whereas specific IgE antibodies to potential skin allergens were less prevalent. Twenty-six children (21.8%) had IgE antibodies to *P. orbiculare,* 14 (11.8%) to *T. rubrum* and 3 (2.5%) to *S. aureus*. Atopic dermatitis in children with one or several RAST positivities was worse, with a more chronic course, higher total eczema score, more frequent distribution in the head-neck-face region and more itch compared to the children without serum detectable IgE antibodies. Severe itch disturbing nightly sleep was the only clinical feature that characterised *P. orbiculare*-positive cases. Allergy to *P. orbiculare* appears to be of little importance in early childhood atopic dermatitis but is likely to carry a poor prognosis. *Key words: fungal allergy; IgE-antibodies; Pityrosporum ovale*.

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S.L. Nordvall, Department of Pediatrics, St. Göran's Children's Hospital, Karolinska Institute, Box 12500, S-11281 Stockholm, Sweden.

Atopic dermatitis (AD) is a common skin disease of unknown etiology. Symptoms of AD may be triggered or aggravated by various factors, such as reduced air humidity, sweating, mechanical and chemical irritants, infections, emotional stress and allergens. The latter include food allergens (1), aero-allergens such as pollens (2), house dust mites (3) and probably allergens belonging to the skin microflora, e.g. *Staphylococcus aureus* and *Pityrosporum orbiculare* (for review see 4). The serum IgE level is frequently elevated, especially in patients with severe AD and concomitant respiratory atopy (5, 6). The importance of IgE in the pathogenesis of AD and the way in which IgE antibodies act, however, still have to be clarified. Recent findings show that IgE is bound to epidermal Langerhans' cells in the skin of AD patients with elevated serum IgE level, whereas IgE is not present on epidermal Langerhans' cells in the skin of patients with respiratory atopy without AD, or in healthy controls (7). A possible role for the epidermal Langerhans' cells bearing allergen-specific IgE is to bind and present allergens to T-lymphocytes, thereby linking the IgE of atopy and immediate type hypersensitivity to the cutaneous T-cell response of delayed type hypersensitivity.

In this context, allergens which constitute a part of the skin microflora, such as lipophilic yeast and *P. ovale,* are particularly interesting. These two Pityrosporum species have a close antigenic relationship, and it is suggested (8) that they represent different stages in a cell cycle of the same species. *P. orbiculare* belongs to the norm skin microflora in adults and is distributed predominantly in seborrhoeic areas such as the scalp, face, chest and upper back (9–11).

Several authors report on atopic sensitization to *P. orbiculare* in patients with AD (12–17), whereas patients with respiratory atopy without AD are only rarely sensitized to the yeast (13, 15–17). The aim of the present investigation was to study the occurrence of sensitization to *P. orbiculare* in children with AD and clinical disease traits in children with such sensitization in the context of sensitization to other allergens.

MATERIAL AND METHODS

Patients

Consecutive cases of children attending the outpatient paediatric clinic of the Department of Dermatology at the Karolinska Hospital, self-referrals, referrals and children undergoing regular follow-up, were investigated. They were required to suffer from AD according to the criteria of Hanifin & Rajka (18). One hundred and nineteen cases aged 4–16 years were included consecutively by a dermatologist (C–FW), and a structured interview of the patient and one parent was performed by one paediatrician (LL). At the same visit a clinical examination of the AD was made. Questions were asked about age at onset of the AD, course of the disease and severity of itching. The latter was appraised by the child's and parent's assessment of nightly itching/scratching and consequent disturbance of sleep according to a three-step ordinal scale: no, mild and severe. Data about atopic heredity, defined as atopy in parents and/or siblings, and other atopic diseases than AD, i.e. bronchial asthma, allergic rhinoconjunctivitis and food allergy were so collected using the routine questionnaire of the Allergy section of the Swedish Paediatric Association, which was reviewed in detail during the interview. The clinical investigation focused on the extension and severity of eczematous skin lesions, scoring the severity in each of twenty different skin regions from 0–3, thus allowing for a total score of 0–60 (19).

Measurement of specific IgE antibodies

Serum was assayed for IgE antibodies to *P. orbiculare, Candida albicans, Dermatophagoides pteronyssinus,* timothy, birch and to mixed discs with common inhalant moulds, animal epithelia and important food allergens using CAP-RAST-FEIA (KABI-Pharmacia AB, Uppsala, Sweden) and the Phadebas RAST (KABI-Pharmacia AB, Uppsala, Sweden) for IgE antibodies to *Trichophyton rubrum* and *Staphylococcus aureus*. Both tests were used in accordance with the recommendations of the manufacturer. The results were expressed in kU/l (CAP-RAST-FEIA) and PRU/ml (RAST) in relation to standard curves.

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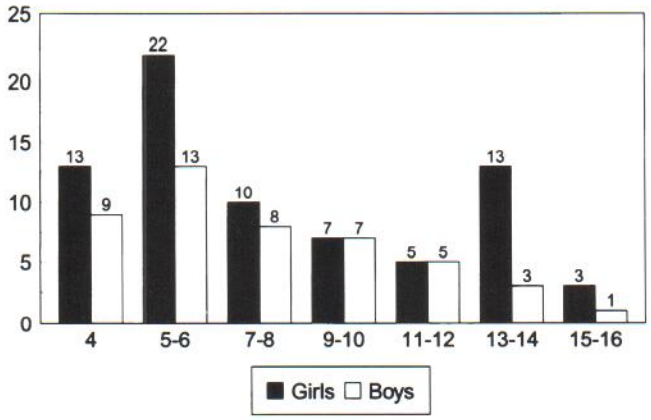

Fig. 1. Age and sex distribution of 119 children with atopic dermatitis.

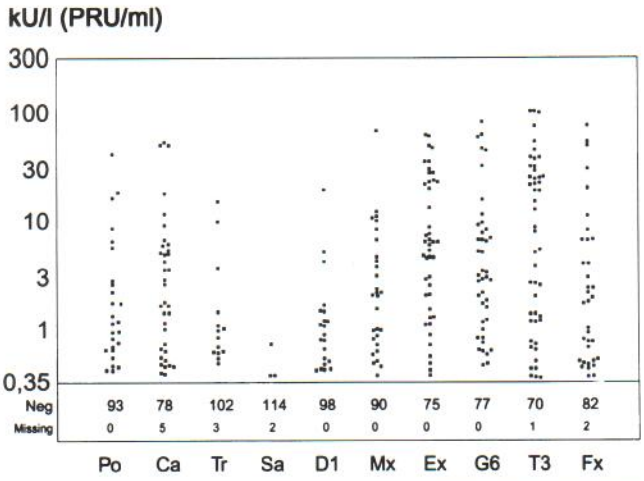

Fig. 2. IgE antibody levels in 119 children with atopic dermatitis measured with CAP-RAST (kU/l) and Phadebas RAST (PRU/ml) (only *Tr* and *Sa*) *Po = P. orbiculare, Ca = C. albicans, Tr = Trichophyton rubrum, Sa = Staphylococcus aureus, Dl = Dermatophagoides pteronyssinus, Mx* = mixed moulds, *Ex* = mixed animal epithelia, *G6* = timothy, *T3* = birch and *Fx* = mixed foods.

Statistical analyses

The Spearman rank test, Mann-Whitney's and chi-square tests were used.

RESULTS

Clinical findings

The study included more girls than boys, 73 versus 46. The median age of the children was 7 years. A detailed account of the age and sex distribution of the children is given in Fig. 1.

Seventy per cent of the children had a family history of AD, i.e. in a parent and/or in a sibling. Fifty-one per cent of the children suffered from a respiratory atopic disease, bronchial asthma in 29%, rhinoconjunctivitis in 46% and both in 24% of the cases. Recurrent episodes of urticaria were reported in 8% of the cases. The onset of AD was in 56% of the cases before 1 year of age. Thirty-seven per cent of the cases reported that they were never free of lesions, and in 43% of the cases severe itch was reported. In the vast majority of the children, the AD was worse in the winter. Sex had no influence on the severity of itching, chronicity, or simultaneous occurrence of bronchial asthma and/or rhinoconjunctivitis.

The median AD score was 8.0 (range 0–29), and slightly higher scores were found in boys than in girls (median 9.0 versus 7.0, ns). This was more evident above 10 years of age; here the median AD score was 11.0 for boys versus 8.0 for girls ($p < 0.05$). Sixty-four per cent of the children had eczematous lesions in the head-neck-face region, 46% on the hands and 27% on the feet. There was no difference between the sexes as regards the distribution of lesions.

Total serum IgE and specific IgE antibodies in serum

The total serum IgE ranged between 2 and 10.100 kU/l, median 95. Girls tended to have higher total serum IgE than boys, median 114 (range 2–10.100) kU/l, compared to 60 (range 2–2900) kU/l (ns), respectively.

The serum levels of IgE antibodies to different allergens are depicted in Fig. 2. Among the RAST-positive children, 34% had IgE antibodies to *P. orbiculare* and 47% to *C. albicans*. IgE antibodies to *T. rubrum* were detected in 18%. A substantial proportion of the children exhibited IgE antibodies to pollens, animal dandruff and/or to foods, whereas only 3 children had low concentrations of IgE antibodies to *S. aureus*. The level of IgE antibodies to any of *P. orbiculare, C. albicans* and *T. rubrum* was generally not as high as that to common inhalant allergens.

Sixty-five per cent exhibited some RAST positivity, among which 29% were positive only to one allergen, 23% to two and 35% to 5 or more of the 10 different allergens. Most of the *P. orbiculare*-positive children had multiple RAST positivities, but one exhibited IgE antibodies only to *P. orbiculare*. Fifty-nine per cent of the 27 children with five or more RAST positivities were *P. orbiculare*-positive. Among children with RAST positivity only to one or two allergens, positivities to pollens were the most common.

Sixteen of the *P. orbiculare*-positive children were girls and 10 boys. Sensitization to *P. orbiculare* did occur at a low age but was more prevalent with increasing age, as was sensitization to

Table I. *Occurrence of IgE antibodies in 119 children with atopic dermatitis in relation to RAST positivity to P. orbiculare (P.o.)*

Number of subjects and per cent within brackets

	RAST-positive $n = 77$		All $n = 119$
	P.o.-pos. $n = 26$	P.o.-neg. $n = 51$	
House dust mite	13 (50)	8 (16)	21 (18)
Animal epithelia	19 (73)	25 (49)	44 (37)
Moulds	17 (65)	12 (24)	29 (24)
Birch	15 (58)	33 (65)	48 (40)
Timothy	14 (54)	28 (55)	42 (35)
Foods	9 (35)	26 (51)	35 (29)
T. rubrum	7 (27)	7 (14)	14 (12)
S. aureus	1 (4)	2 (4)	3 (2.5)
C. albicans	19 (73)	17 (33)	36 (30)

Table II. *Clinical characterisation of 119 children with atopic dermatitis in relation to RAST positivity to P. orbiculare (P.o.) and other allergens*

Proportion of patients in per cent within brackets

Clinical characteristic	RAST-positive $n = 77$		RAST-negative $n = 42$
	P.o.-pos. $n = 26$	P.o.-neg. $n = 51$	
Age (mean ± SD)	9.9	7.6	7.1
Sex (M;F)	10; 16	18; 33	18; 24
AD score	12.2	8.5	7.1
Chronic course	14 (54)	20 (39)	10 (24)
Severe nightly itch	19 (73)	22 (43)	11 (26)
Head-neck-area distribution	22 (85)	36 (71)	18 (43)
Heredity for AD	19 (73)	38 (75)	26 (62)
Onset of AD (<1 year of age)	16 (62)	34 (67)	16 (38)
Asthma	12 (46)	17 (33)	6 (14)
Rhinitis and/or Conjunctivitis	18 (69)	30 (59)	7 (17)
Urticaria (>5 times)	3 (12)	5 (10)	1 (2)
Oral antibiotics (≥5 times)	4 (15)	6 (12)	1 (2)
Pneumonia (>3 times)	1 (4)	3 (6)	1 (2)
Diaper dermatitis	7 (27)	24 (47)	17 (40)

all allergens with the exception of foods and grass pollens. Above 10 years of age 43% of all children and 2/3 of those with any RAST positivity were *P. orbiculare* RAST-positive. *P. orbiculare*-positive children were more frequently positive to house dust mites, inhalant moulds and *T. rubrum* than were *P. orbiculare*-negative children, who more frequently exhibited IgE antibodies to birch, timothy and foods (Table I). These associations may well be age-dependent. Thus there was a qualitative association between sensitization to *P. orbiculare* and house dust mite but there was no corresponding quantitative correlation between the levels of the respective IgE antibodies.

The RAST-negative children exhibited a median total serum IgE of 18.5, range 2–930 kU/l, as compared to 208 (6–10.100) kU/l in the children of the RAST-positive group ($p < 0.001$). Among the latter, *P. orbiculare*-positive children had significantly higher median total IgE ($p < 0.001$) than *P. orbiculare*-negative children, 497 (23–10.100) and 141 (6–2900) kU/l, respectively.

Clinical correlates to specific serum IgE antibodies

The RAST-positive children's AD was generally worse than that of the RAST-negative children (Table II). This was true for the AD score ($p < 0.01$), chronicity ($p < 0.01$) and occurrence of severe itching/scratching ($p < 0.05$). Head-neck-face distribution was more common ($p < 0.001$), and the onset of the AD earlier in life ($p < 0.05$) in the RAST-positive than the RAST-negative cases. Infections of the AD requiring oral treatment with antibiotics also tended to be more common among the RAST-positive than the RAST-negative children. Further the RAST-positive children more frequently suffered from bronchial asthma ($p < 0.02$) and allergic rhinoconjunctivitis ($p < 10^{-6}$). Eight per cent of the RAST-positive children reported deterioration of the AD during the period April to July, while none of the RAST-negative children's AD worsened during that period.

The AD of the 26 *P. orbiculare* RAST-positive children was more severe than that of the *P. orbiculare* RAST-negative children. The former children's AD more often tended to be distributed in the head-neck-face region, but this was true also for the lesions of the house dust mite-, *C. albicans*- and mould-positive children. Itching/scratching with disturbance of nightly sleep was the only clinical feature which characterized *P. orbiculare*-positive children when compared with the children with other RAST-positivities; nightly itch was thus significantly ($p < 0.05$) more severe in the former than in the latter children, but there was a tendency in that direction also for positivity to house dust mites. Seven children who were RAST-positive both to *P. orbiculare*, *T. rubrum* and *C. albicans* all exhibited a high AD score, 15 in median.

DISCUSSION

Atopy was originally defined by Coca & Cooke (20) by the occurrence of skin test immediate reactions to common inhalant allergens. A modern version of the definition could include the occurrence of serum IgE antibodies to inhalant allergens and/or foods. Atopy is closely associated with the atopic diseases, and it is characteristic that different disease manifestations appear in the same individual. There is little doubt that the IgE-mediated allergic reaction is of major pathogenic importance in respiratory allergy, i.e. bronchial asthma and allergic rhinitis, whereas the role of IgE in the pathogenesis of AD still is unclear (21, 22). It is thus held by many that IgE-mediated allergies are merely associated but not causally related to the pathogenic events in AD. It is well known that food allergens, e.g. cow's milk, may elicit and worsen AD in children allergic to cow's milk (23, 24). Flare-ups of AD in pollen-sensitized patients during heavy pollen exposure may also occur (2). Much interest has also been focused on the role of exposure to house dust mite in AD (25, 26). Yet, it is quite evident that mechanisms other than the atopic allergic are important in the pathogenesis of AD (21).

In the present study, a large number of AD children of various ages were studied. The fact that the patients were sampled from a hospital clinic may, however, to some extent have yielded a biased patient selection. Thus, both the higher proportion of girls and their lower AD scores may be the consequence of a higher propensity in girls than in boys to attend medical care. Yet, as is understood from the varying symptom scores, there were not only children with severe, but so very mild disease, which may well be a consequence of the possibility of self-referral to this outpatient clinic. Thus, as regards the severity of the AD, the cases appear to represent all degrees of severity of AD.

Only 26 of the 119 cldren with AD were RAST-positive to *P. orbiculare*. The proportion of *P. orbiculare* RAST-positive children increased with age, which can well be a consequence of a general age-dependent phenomenon but may also be explained by the fact that the degree of skin colonisation by *P. orbiculare* varies with age (27). Thus in studies in this country, no growth of *P. orbiculare* was found in the skin of children under 5 years

of age (10) and positive cultures in only 5% of children aged 0–10 years, as compared to 90% in children and young adults aged 11–21 years (12). In the latter study colonisation in patients with AD with *P. orbiculare* was not found to be more common than in healthy subjects (12). Interestingly the low occurrence of colonisation to *P. orbiculare* contrasts to data obtained in a different climate, Mexico, where positive cultures for *P. orbiculare* obtained from healthy-looking skin of infants were found in as many as 53% of healthy children aged 1–24 months, (27) a feature which would possibly also lead to a high frequency of sensitization in eczematous patients in that part of the world.

The notion that IgE-mediated allergy to *P. orbiculare* is of significance in the pathogenesis of AD lends support from studies showing that sensitization to this yeast occurs almost exclusively in patients with AD (15), preferentially when in the head-neck-face region (13), i.e. one of the predilection areas for growth of the yeast, and that the yeast is of almost ubiquitous occurrence in the skin of adult patients (28). In the present study emphasis was put on the relationship between atopic sensitization to *P. orbiculare* and the clinical characteristics in childhood of AD. Children with atopic sensitization had exhibited more severe dermatitis than children without, which does not, however, necessarily indicate a causal pathogenic relationship. Among children with RAST positivities cases with sensitization to *P. orbiculare* presented with the most severe AD. This was particularly true for severe itching, which was, however, not specific for sensitization to *P. orbiculare* but applied also to some extent to sensitization to house dust mites. Our study cannot firmly establish that allergy to *P. orbiculare* is of importance in the pathogenesis of childhood AD. Rather, sensitization to *P. orbiculare* appears to be a marker of severe atopy, just as is sensitization to inhalant moulds and house dust mites in this part of the world, where mite infestation is scarce (29, 30). Apart from severe nightly itch, disease traits with some specificity for atopic sensitization to *P. orbiculare* in children with AD were lacking, which may well be explained by poor exposure in childhood to this yeast. Yet, allergy to *P. orbiculare* may be of importance in teenagers, who were only poorly represented in this study, and adults. Sensitization to *P. orbiculare* in children may thus well carry a poor prognosis for adulthood AD.

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