Allergology International (2001) **50**: 239–245

Original Article

Mold-specific IgE antibodies in relation to exposure and skin test data in schoolchildren

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Abstract

Background: The purpose of the present study was to compare mold specific IgE results with skin test and exposure data, as well as in relation to asthma and other allergic manifestations.

Methods: We performed skin prick tests (SPT) to 13 molds in 341 children from six schools and studied the microbial status of all school buildings. Subsequently, mold specific IgE was measured by enzyme immunoassay (EIA) to 10 molds in 31 of those children with a positive (≥ 3 mm) or weak SPT reaction (1–2 mm) and in 62 age- and sex-matched controls with no such reactions.

Results: Mold-specific IgE was elevated by EIA (> 0.35 IU/mL) to at least one of the 10 studied species in 12 children (39%) with and in two children (3%) without skin test reactions. The calculated prevalence of elevated mold-specific IgE was 5% in the non-selected and 10% in children selected by respiratory morbidity. Six children had IgE to the dampness-indicative mold *Aspergillus fumigatus*, five children had IgE to the common outdoor mold *Cladosporium herbarum* and four children had IgE to the uncommon, but highly allergenic, indoor mold *Rhizopus nigricans*. All 14 children who had elevated IgE to molds were boys, 13 had atopy by skin tests and 12 had either asthma or had wheezed. However, no species-specific association was found between IgE or SPT responses and exposure to molds.

Conclusions: Mold allergy, as assessed by IgE measurements or skin tests, is rare in children. School-aged asthmatic boys having exposed to indoor air dampness seem to form a susceptible group for mold allergy, being at risk for worsening of their asthma.

Key words: allergy, asthma, gender, IgE, moisture problem, mold, mold sensitization, schoolchildren, skin prick tests.

Introduction

Moisture damage and mold growth in a building may lead to sensitization of its occupants, resulting mainly in respiratory symptoms and pulmonary disorders.[1–3] The mechanism by which sensitization to molds takes place has remained obscure. Although symptoms are more common in atopic than in non-atopic persons, the role of atopy in sensitization is poorly understood.[4] We performed skin prick tests (SPT) to 13 molds in two separate cohorts of schoolchildren[5,6] and found that positive responses were rare, being present in 2.4–5% of children. In two other studies, IgE to molds was demonstrable in 10% of children with chronic respiratory symptoms and in up to 38% of asthmatic children.[7,8] However, in neither study was there any association with dampness or mold exposure in indoor air. In contrast, many studies have described a significant relationship between mold sensitization and asthma or other respiratory manifestations.[3,5,7,9]

In the present study, we report the results of specific IgE antibody determinations to 10 molds in the two

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Received 5 October 2000. Accepted for publication 23 April 2001.

aforementioned cohorts of schoolchildren. The aim of the study was to evaluate the role of IgE-mediated sensitization to molds in children exposed to moisture and molds in school buildings, with special attention paid to exposure data, SPT results and the presence of asthma or allergy.

METHODS

Skin prick tests were performed to 13 molds in 341 children, aged between 7 and 13 years, from six different elementary schools in our two previous studies.[5,6] The study designs, including enrolment of children and collection of clinical and exposure data, have been published in more detail elsewhere.[5,6] In brief, 133 children (99 from three moisture-problem schools (index schools) and 34 from a healthy control school) attended the study in Kiuruvesi and 212 children (170 from a moisture-problem school and 42 from a healthy control school) attended the study in Siilinjärvi. The subjects of the present study were selected on the basis of SPT responses to molds, consisting of 93 children from these two cohorts, 31 with positive or weak and 62 without any SPT reactions to molds. Specific IgE antibodies to 10 molds were analyzed in 54 children from Kiuruvesi (48 were from moisture-problem schools)[5] and in 39 children from Siilinjärvi (30 were from a moisture-problem school).[6]

The six school buildings were characterized by technical and microbiological examinations, as described elsewhere.[5,6] These examinations included inspection of the building for signs of water damage, visible moisture or mold growth. Surface moisture recorders were used to assess the moisture content of the structures. No dismantling of the structures was done. In all six school buildings, the microbial sampling was made from the air and surfaces of the buildings, as described elsewhere.[5,6] The total concentrations of airborne viable fungi were measured. In addition, the fungi were cultivated from surface samples. Visible signs of moisture problems were seen in all four moisture-problem schools and visible fungal growth was observed in all but one index schools, but not in the two control schools. The mean concentrations of total fungi varied from 53 to 150 c.f.u./m^3 in the three index schools in Kiuruvesi compared with 53 c.f.u./m^3 in the control school. These respective values were 21 and 4 c.f.u./m^3 in Siilinjärvi. In total, 29 fungal species were found in the three index schools in Kiuruvesi compared with 20 species in the control school.[10] The respective figures for Siilinjärvi were 31 and 15.[11]

The data on asthma and allergy were based on clinical examination in both cohorts, supplemented by interviewing the parents in Kiuruvesi[5] and by questionnaires filled in by the parents in Siilinjärvi.[6] In addition, the medical cards of the health-care centers were available in both studies. Chronic, prolonged or repeated respiratory manifestations, if present, were classified into three groups: asthma, wheezing symptoms and cough symptoms.[5,6] The diagnosis of asthma in each case was confirmed from the medical cards of the health-care center, regional hospital or central university hospital. Thus, asthma was doctor diagnosed and wheezing parent reported.

Allergic manifestations were classified into allergic rhinitis, allergic conjunctivitis and atopic eczema. In addition, SPT results to 11 common inhalation allergens and to 13 fungal antigens produced by ALK (Allergologiska Laboratorium, Copenhagen, Denmark) were available in all children; *Aspergillus fumigatus, Fusarium roseum, Phoma herbarum* and *Rhodotorula rubra* were included as dampness-indicative molds.[12] With the exception of *Phoma* spp. and *R. rubra*, all other molds with SPT extracts available were also found in the moisture-problem schools of the present study. The criteria of atopic manifestations, as well as the performance, interpretation and results of the SPT have been published elsewhere.[5,6] In SPT, the largest diameter of the wheal was measured 15 min after allergen application. The reaction was considered as positive if the largest diameter was > 3 mm or if the shape of the weal was irregular with pseudopodia.

As published recently, 11 children had positive (≥ 3 mm) and 20 children had weak (1–2 mm) reactions to molds.[5,6] These 31 children form the index cases of the present study. Eighteen percent of children were aged 7–8 years, 36% were aged 9–10 years and 45% were aged 11–13 and there were 22 (71%) boys and nine girls. Serum mold-specific IgE concentrations were determined in these 31 index children and in an additional 62 age- and sex-matched control children attending the same schools who had negative SPT reactions to molds. Therefore, mold-specific IgE concentrations were determined in a total of 93 children to mycelial antigens of 10 molds: *Penicillium notatum* (m1), *Cladosporium herbarum* (m2), *A. fumigatus* (m3), *Mucor racemosus* (m4), *Alternaria alternata* (m6), *Botrytis cinerea* (m7), *Rhizopus nigricans* (m11), *Aureobasidium pullulans* (m12), *Fusarium moniliforme* (m9) and *Phoma betae* (m13). Dampness-indicative molds were *A. fumigatus, F. moniliforme* and *P. betae*.[12–14] With the exception of

Phoma spp., all other molds with a specific IgE test available were also found in the moisture-problem schools of the present study.

Serum samples of children were stored at –20°C until analyzed for IgE antibodies. The measurements of allergen-specific IgE antibodies were performed according to the instructions of the manufacturer for the AlaSTAT (Diagnostics Products, Los Angeles, CA, USA). The AlaSTAT is a kinetic enzyme-labeled immunometric assay (EIA) that was conducted in the following manner. A serum sample (50 μL) was added, with a ligand-labeled specific allergen (50 μL) in a liquid format, to the wells of a microplate and incubated for 1 h at room temperature with agitation. The next addition of an antiligand (50 μL) was used to create a bridge between the allergen/IgE complexes and the ligand-coated wells during a second 1 h incubation. After washing, 200 μL peroxidase-labeled monoclonal anti-IgE antibody was added, and the mixture was incubated for 1 h at room temperature and washed. A chromogenic indicator (3,3′,5,5′-tetramethylbenzidine) in a buffered hydrogen peroxide solution was then added and the rate of color development was ascertained by monitoring the product using a kinetic analyzer, measuring for 5 min at a wavelength of 650 nm. The reaction rate is directly related to the concentration of allergen-specific IgE, which is expressed in IU/mL (kU/L). The IU is determined by using the World Health Organization's second international reference preparation for human serum IgE, no. 72/502. An IgE concentration of 0.35 IU/mL or more was regarded as positive. If the reaction rate was 50–100% of the rate corresponding that concentration, the result was regarded as uncertain. A reaction rate < 50% of the limiting value was regarded as negative.

The study protocol was approved by the Ethics Committee of Kuopio University Hospital. Informed written consent was obtained from the parents of all children.

Data were analyzed using the SPSS statistical package (SPSS Inc., Chicago, IL, USA). Chi-squared and Fisher's exact tests were used to analyze the significance of differences between groups. Multivariate logistic regression was used to analyze the association between specific IgE antibodies and asthma and/or wheezing symptoms.

Results

Serum mold-specific IgE to at least one of the 10 species studied was elevated (> 0.35 IU/mL) in 14 (15%) children; 12 were index children and only two were control children (Table 1). Among these children, six children had specific IgE antibodies to *A. fumigatus*, five had specific IgE antibodies to *C. herbarum* and four had specific IgE antibodies to *R. nigricans*. In addition, specific IgE to all other molds, except *P. betae*, was found in at least one child. There were seven children (50%) with specific IgE to dampness-indicative molds. In addition, there were uncertain IgE concentrations in 17 children (18%).

An elevated IgE concentration was present in seven of 11 children (64%) with a positive SPT reaction and in five of 20 children (25%) with a weak SPT reaction to molds (Table 2). The figure was 3% in the SPT-negative control children. Thus, 12 of 14 children (86%) with elevated IgE had either a positive or weak SPT reaction. In contrast, 76% of 17 children with uncertain IgE values were SPT negative. This figure was equal (76%) to the number of children with negative IgE results.

Both SPT and IgE determinations were examined for 10 molds; eight molds were the same species in both tests and the two non-identical molds (*Fusarium* spp. and *Phoma* spp.) were of the same genus. The two methods gave at least one concordant positive result in four of 11 SPT-positive children (36%) and in three children (16%) if the SPT gave weak responses, respectively (data not shown). These four cases form 29% of the 14 IgE-positive children.

Positive mold-specific IgE was significantly associated with asthma and wheezing (Table 3), but not with cough

Table 1 Serum mold-specific IgE antibodies to 10 molds in 93 school children

Mold	Serum mold-specific IgE (no. A/B)		
	Positive	Uncertain	Negative
*Aspergillus fumigatus**	5/1	3/3	23/58
*Fusarium moniliforme**	1/0	2/0	28/62
*Phoma betae**	0/0	2/0	29/62
Alternaria alternata	3/0	2/1	26/59
Aureobasidium pullulans	1/0	1/0	29/62
Botrytis cinerea	2/0	1/1	28/61
Cladosporium herbarum	5/0	1/0	25/62
Mucor racemosus	2/0	3/4	26/58
Penicillium notatum	2/0	5/5	24/57
Rhizopus nigricans	3/1	7/6	21/55
Total	12/2	4/13	15/47

Data (no. A/B) show the number of cases, where A is the number of skin prick test (SPT)-positive ($n = 11$) or weakly ($n = 20$) positive index cases and B is the number of SPT negative ($n = 62$) age- and sex-matched cases.

Positive reactions were defined as levels over 0.35 IU/mL, negative and uncertains levels are defined in the text.

*Moisture indicative molds.

Table 2 Association between IgE antibodies and skin test reactions to molds in 31 index and 62 control subjects

SPT reaction to molds	No. with mold-specific IgE antibodies (%)		
	Positive	Uncertain	Negative
Index subjects			
Positive reactions ($n = 11$)	7 (64)*	1 (9)	3 (27)
Weak reactions ($n = 20$)	5 (25)†	3 (15)	12 (60)
Control subjects			
No reactions ($n = 62$)	2 (3)	13 (21)	47 (76)

*$P < 0.001$ compared with subjects with weak or negative skin prick test (SPT) reactions; †$P < 0.01$ compared with subjects with negative SPT reactions.

Data on mold-specific IgE antibodies are based on the highest mold-specific IgE concentration.

For more details regarding subjects refer to Methods.

Table 3 Serum IgE antibodies to 10 molds in relation to clinical and skin test data among 93 schoolchildren

Clinical data	All children ($n = 93$)	IgE elevated ($n = 14$)	*P*	IgE not elevated ($n = 79$)
Respiratory morbidity	34 (37%)	12 (86%)	< 0.05	22 (28%)
Asthma	15	6†		9
Wheezing	19	6*		13
Clinical atopy	35 (38%)	10 (71%)	< 0.01	25 (32%)
Rhinoconjuntivitis	20	7†		13
Eczema	29	8*		21
SPT reactivity	48 (52%)	13 (93%)	< 0.001	35 (44%)
Danders	30	10†		20
Pollens	38	12†		26
Mites	15	6†		9

†$P < 0.01$, *$P < 0.05$ compared with children with no respiratory disorders, atopy or skin prick test (SPT) reactivity to common inhalation allergens.

symptoms (data not shown). All 14 children with elevated IgE to molds were boys and 12 (86%) had asthma or had wheezed. In these cases, the risk was 5.8-fold for asthma (95% confidence interval (CI) 1.7–20.7; $P < 0.01$) and 15.6-fold for asthma or wheezing (95% CI 3.2–75.1; $P < 0.001$). Children with other allergic manifestations, such as allergic rhinitis, conjunctivitis or eczema, had significantly more often IgE antibodies to molds than nonatopic children (29 *vs* 7%, respectively; $P < 0.001$). In addition, sensitization to common inhalation allergens in SPT and serum specific IgE to molds was also significantly related (Table 3).

Fifteen of 93 children (16%) had positive SPT reactions to house dust mites; 14 were to *Dermatophagoides pteronyssinus* and eight were to *Dermatophagoides farinae*. These responses were more common in mold-specific IgE-positive (43%) than negative children (43 *vs* 11%, respectively; $P < 0.01$; Table 3). The respective figures for children with positive, weak and negative SPT reactions to molds were four (36%; $P < 0.05$), seven (35%; $P < 0.01$) and four (6%).

Fifteen of 18 children (84%) with elevated mold-specific IgE or positive SPT reactions to molds had been exposed to dampness in their schools. The figure was the same (83%) in the total group of 93 children. The SPT and IgE responses to molds among children exposed at school and non-exposed children are presented in Table 4. No significant fungus-specific associations were seen between these responses and exposure.

In the Kiuruvesi group, 14% of children had positive or weak SPT reactions to molds. In the Siilinjärvi group, the corresponding figure was 6%. In the first group, mold-specific IgE was elevated in 39% of children with SPT responses and in none of the children with no response. The respective figures were 38 and 8% in the second group. From these figures, we calculated the estimated proportion of children with elevated mold-specific IgE in the original cohorts and concluded that it was 5% in the

Table 4 Skin prick test and serum mold-specific IgE reactivity among in school exposed and non-exposed children in relation to mold-specific exposure data of the six school buildings

Microbes identified	No. children tested	No. SPT positive	No. IgE positive	% SPT or IgE positive
Aspergillus fumigatus	30/63	1/3	2/4	10/9
Fusarium spp.	30/63	0/4	1/0	3/6
Alternaria spp.	54/39	0/0	0/3	0/8
Aureobasidium pullulans	66/27	1/0	1/0	3/0
Botrytis spp.	9/84	0/0	1/1	11/1
Cladosporium spp.	84/9	3/1	4/1	6/11
Mucor spp.	42/51	0/1	1/1	2/4
Penicillium spp.	93/0	2/0	2/0	4/0
Rhizopus spp.	0/93	0/1	0/4	0/4

Data show the number of children who were exposed to molds in school buildings/number of children who were not exposed to molds in school buildings. Children were considered to be exposed to a specific mold if the mold was found either in three or more air samples and/or surface samples and/or building material of the corresponding building.

An SPT positive response was defined as a ≥ 3 mm response to molds; an IgE positive response was > 0.35 IU/mL.

In total, 37 different molds were identified in school buildings[20,21] and allergen extracts for skin prick tests (SPT) and IgE measurements were available for nine (25%). *Aspergillus fumigatus, Fusarium* spp. *and Phoma* spp. were moisture-indicative molds; *Phoma* spp. were not identified in any building.

non-selected Kiuruvesi cohort and 10% in the Siilinjärvi cohort selected on the basis of chronic or repeated respiratory morbidity.

Discussion

In the present study, we measured mold-specific IgE antibodies to mycelial antigens of 10 molds. The main result of the present study was that specific IgE antibodies to molds are rare at school age, the estimated prevalence being 5% in non-selected children and 10% in children selected by chronic or repeated respiratory morbidity. Over 75% of children attended schools with documented water damage that, at least theoretically, increases the risk for sensitization to molds. Verhoeff *et al.*[7] have reported that 10% of children with long-term respiratory symptoms and only 1% of healthy children had significant serum concentrations of mold-specific IgE.

The majority (86%) of sensitized children suffered from asthma or wheezing and, correspondingly, up to 35% of children with asthma or wheezing had IgE antibodies to molds. The figure is rather similar to that of 38% reported in Swedish children with severe asthma.[8] In addition, mold-specific IgE measured by radioallergosorbent test has been much more common among asthmatic than non-asthmatic children.[5,15,16] Wickman *et al.*[9] found that sensitization to molds, although taking place rarely, was a very strong risk factor for asthma. In the present study, elevated mold-specific IgE carried a six-fold risk for asthma and a 16-fold risk for asthma or wheezing. However, although the risk is high, it only means an association, not any causal relationship. In addition, IgE antibodies to molds were common in children with other allergic manifestations, as well as in those with SPT reactions to common inhalation allergens, including house dust mites.[15] In our country, allergy to mites is rare due to the cold climate and the need for artificial heating of the buildings, leading to a dry indoor air and small mite concentrations. Thus, sensitization to molds occurs mostly in individuals with a high potential to become sensitized to inhalation allergens[4] and, further, with a high risk for asthma.

Cladosporium is the most common sensitizing outdoor mold in northern Europe, followed by *Penicillium* and *Aspergillus*.[17–19] The order has been the same in studies assessing the occurence of and sensitization to indoor molds,[16,18] including the moisture and mold-problem schools in the present study.[10,11] *Alternaria alternata* is a common outdoor mold in southern Europe,[17,20,21] occuring in our country both in outdoor and indoor air during summertime.[22] *Rhizopus nigricans* is an indoor mold with a high allergenic potential.[20] These five molds accounted for the majority (75%) of positive IgE responses in the present study, although most responses to *Penicillium* and *R. nigricans* were in the uncertain region. The results of the SPT and IgE studies are greatly dependent on the selection of allergens in the test panels. In the present study, commercial extracts were used and they covered only a minority of molds identified in the indoor air and, in particular, in buildings with moisture problems.[10,11]

This explains, at least in part, the poor association between SPT and IgE results and exposure data. Thus, the true prevalence of mold allergy, especially allergy to dampness-indicative or other molds reflecting indoor air problems, may have been underestimated.

Iversen *et al.*[4] have suggested that the absolute amount of a certain mold in the environment is not related to IgE synthesis or sensitization to that mold. Here, too, IgE antibodies to molds were rather rare, even though exposure to dampness and/or molds had taken place in the school environment. In addition, children may have been exposed to molds in many different environments, not only at school. Many fungi produce variable amounts of spores and other products over time, leading to different levels of exposure at different times.[23–25] In addition, mold spore concentrations in indoor air are generally rather low in residential houses or buildings, such as schools, even though there are visible signs of moisture damage or visible mold growth in the structures or surfaces,[19,26] as observed in the schools in the present study.[10,11] Thus, it is difficult to measure the real exposures due to indoor dampness or fungal growth and this difficulty may lead to the underestimation of the problem, which seems to be harmful for a subpopulation, namely children prone to allergic asthma.[3,4,9]

It has been suggested that IgE assays are not optimal to study atopic sensitization to molds, being, for example, less sensitive than SPT.[7,15,20] However, mold allergy has been equally rare in our previous skin test studies.[5,6] Currently, only non-standardized allergen extracts are available for both SPT and IgE assays and, as also seen in the present paper, the agreement between SPT and IgE responses is less than 30%. Even in the case of the same molds, the allergens used in SPT and IgE measurements may contain different components. In accordance with the results of Nordvall *et al.*,[8] all children who were IgE positive to molds were boys, although girls usually report more symptoms of mold exposure.[6] The boys were over 10 years of age, had either asthma or had wheezed, reacted to molds in both SPT and IgE determinations and, with the exception of one case, reacted to moisture-indicative molds. Thus, sensitivity to several molds is rare but, when present, it tends to cluster in certain patients.[4,8,15,16,24] Although mold allergy was rare, we were able to identify a risk group, namely boys over 10 years of age with multiple allergies and prone to asthma, exposed to moisture and mold in the school environment.[9]

Acknowledgments

The authors are grateful to Ms Raija Juntunen, specialized nurse, for performing the skin testing on the children, Ms Jaana Liukkonen, MSc, and Ms Eeva Toikkanen for their skillful assistance with serum IgE antibody analyses, and Mr Mikko Vahteristo, MSc, for his advice on statistical analyses. The study was financially supported by grants from North-Savo regional Fund of The Finnish Cultural Foundation, Kerttu and Kalle Viikki's Fund, Emil Aaltonen's Fund, SYTTY-program of Academy of Finland and The Environment, Health and Society-program of the University of Kuopio, Finland.

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