

Bronchial hyper-responsiveness in selective IgA deficiency

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Secretory IgA in mucosal secretions has a broad protective function. The insufficient protection provided by the respiratory mucosa in children with selective IgA deficiency (sIgAD) might facilitate the development of bronchial hyper-responsiveness (BHR) and consequently asthma symptoms. This study was conducted to clarify the prevalence of BHR in sIgAD children and the relationship with atopic status. A cohort of 20 children (group A) aged 6.4–20.1 yr (median: 12.6) with sIgAD (serum IgA < 6 mg/dl) were evaluated for BHR using inhaled hypertonic saline test as well as for atopy by skin prick testing (SPT) to eight common aero-allergens. Seventy other children with normal levels of serum IgA, but sensitized to aero-allergens (group B) and 102 with normal IgA and negative SPTs (group C) were also evaluated. Baseline spirometry demonstrated that forced vital capacity (FVC) values in group A were significantly lower than in C. Forced expiratory volume in 1 s values were similar in all groups, but impairment of the forced expiratory flow over the middle half of the FVC was detected in group B. The prevalence of BHR was similar among group A (30.0%) and group B (35.7%) ($p = 0.79$) but they differed from group C (5.9%) ($p = 0.005$). An association between BHR and reported current ($p = 0.001$) but not lifetime asthma symptoms among group A was also observed. There was no association between atopy and BHR in group A but only to mites' sensitization ($p = 0.03$). In conclusion, these results indicate that sIgAD constitutes a risk factor for development of BHR but it appears to be related to sensitization to mites.

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Secretory IgA in mucosal secretions has a broad protective function. It can bind antigens, thereby limiting their absorption, inhibiting bacterial attachment to mucosal surfaces, and neutralizing a variety of viruses that might otherwise gain access to the body through mucosal surfaces. Selective IgA deficiency (sIgAD), even if transient, is frequently associated with a high susceptibility to recurrent respiratory tract infections (1–5). The mucosa appears to be less protected against pathogens and more vulnerable, but this is more pronounced in cases of associated IgG subclass deficiency in which the development of bronchiectasis is not rare (1, 6).

Low levels of serum IgA have been reported to be associated with an increased prevalence of

atopy and allergic diseases (4, 5, 7), but there are inconsistent reports as well (8, 9). Studies in the murine model provide conflicting data. The mucosa of IgA-deficient mice has been found devoid of IgA-producing cells, but with an increased number of IgG and especially IgM-producing cells; whereas serum IgE levels were substantially lower than in non-IgA-deficient mice (10). On the contrary, other data show that partial IgA-deficiency in mice with transforming growth factor- β type-1 deficiency display Th₂-type reaction profile (11).

Bronchial hyper-responsiveness (BHR) is considered to be the result of perinatal events, recurrent infections, asthma, allergic sensitization, and environmental determinants such as

cold, smoking, pollution (12–14). It has also been related to the transient absence of salivary IgA in children who do not develop asthma or atopy (15). It is considered that these subjects with transient IgA deficiency may subsequently present with an inappropriate inflammatory response characterized by mucosal hyporeactivity which in turn leads to BHR (15). Persistent sIgAD therefore, could be also a high risk factor as the protective function is impaired.

A considerable proportion of cases with sIgAD develop compensatory mechanisms and show no signs of illness, whereas at least 50% of symptomatic cases will eventually recover when older or as adults (2, 16). However, it is not well known if these otherwise healthy subjects have a different degree of bronchial responsiveness. Therefore this study was conducted, to clarify the prevalence of BHR in children with sIgAD and the relationship with the atopic status.

Patients and methods

Study population

Three groups of children were enrolled in the study (Table 1). Group A consisted of 20 children aged 6.4–20.1 yr (median: 12.6) with sIgAD. Eighteen of them were consecutively presented with recurrent respiratory or other allergic symptoms to the Allergy-Pulmonology Department of Penteli Children's Hospital between May 1995 and April 2003. The other two children were asymptomatic, diagnosed by chance during a screening test. sIgAD was diagnosed if the serum IgA concentration was less than 6 mg/dl

during three or more consecutive evaluations every 3–4 months, with normal levels of other immunoglobulin classes and the diagnosis was established only when subjects were at least 6-year old.

Groups B and C consisted of 70 and 102 schoolchildren respectively recruited from a general population sample. They were matched for age with group A and they consented to be evaluated. Group B schoolchildren were randomly selected and their levels of serum IgA were within normal limits, but they were all sensitized to aeroallergens. Group C consisted of children with normal levels of IgA, but not sensitized to any allergen we tested, regardless of their asthmatic symptomatology. Children with diagnosed or suspected cystic fibrosis, primary ciliary dyskinesia, myoskeletal abnormalities or a history of bronchopulmonary dysplasia were excluded.

Evaluation

Patients' follow up and review for the study's purposes as well as schoolchildren evaluation were performed between February 2002 and September 2003. The parents or guardians of each participating subject provided written informed consent to take part in the study by means of detailed medical history, physical examination, skin prick testing (SPT), spirometry, hypertonic saline inhalation bronchial challenge and a complete self-administered questionnaire.

Questionnaire

The questions included the ISAAC core questions on symptoms of asthma, allergic rhinitis, and atopic eczema. Family atopic history, household heating and passive smoking were also recorded.

Infection profile was detected in all aIgAD cases retrospectively by analyzing our notes or the family physician's reports and the use of antibiotics. Recurrent infections were defined as being more than six episodes of upper respiratory tract infections and/or more than three lower respiratory tract infections in the previous year (6).

Spirometry – hypertonic saline challenge

Lung function testing was performed according to the standards of the American Thoracic Society (17). Flow-volume curves were obtained using a computerized pneumotachograph

Table 1. Demographic data and characteristics of the study groups

	Group A (n = 20)	Group B (n = 70)	Group C (n = 102)	p Value
Male (%)	12 (60)	44 (63)	42 (41)	0.01
Median age (range)	12.6 (6.4–20.1)	12.1 (7.7–16.1)	12.3 (8.4–15.7)	0.96
Atopic family history (%)	11 (55)	55 (78.6)	16 (15.7)	0.001
Passive smoking (%)	10 (50)	39 (55.7)	69 (67.6)	0.15
Central house heating (%)	17 (85)	56 (80.0)	81 (79.4)	0.98
Asthma – lifetime (%)	17 (85)	26 (37.1)	15 (14.7)	0.001
Asthma – Current	6 (30)	17 (24.3)	10 (9.8)	0.04
Chronic rhinitis	12 (60)	22 (31.4)	27 (26.4)	0.01
Eczema	2 (10)	25 (35.8)	16 (15.7)	0.01
Sensitization (%)	11 (55)	70 (100)	–	
Mites	6 (30)	27 (38.6)	–	0.60
Alternaria alternata	1 (5)	7 (10.0)	–	0.67
Seasonal	6 (30)	47 (67.1)	–	0.50
Pets	5 (25)	21 (30.0)	–	0.78
FVC (% predicted)	92.6 ± 6.5	96.0 ± 8.9	99.1 ± 6.6	0.02
FEV ₁ (% predicted)	95 ± 7.3	97.1 ± 7.4	99.3 ± 7.1	0.22
FEF ₅₀ (% predicted)	86 ± 14.7	75.9 ± 16.5	83.0 ± 10.6	0.006

(Vicatet P2a, Mijndhardt). Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁) and forced expiratory flow over the middle half of the FVC (FEF₅₀) were recorded. Spirometry was deferred if the child had suffered a respiratory tract infection within 3 wk or had used a bronchodilator within 12 h. Values were expressed as percentage of predicted for gender and height (18).

Bronchial responsiveness assessment was only performed when FEV₁ values were > 75% of the predicted value. The children inhaled hyperosmolar saline (4.5%) using an ultrasound nebuliser for periods of increasing duration according to Riedler et al. protocol (19). Positive response was defined as a 15% or greater fall in FEV₁ compared with the pre-saline value. The provocative test was done between February and March, as well as August and September of 2002 and 2003 between 9 am and 1 pm. Additionally, it was performed during the children's asymptomatic periods or at least 6 wk after acute respiratory symptomatology. Asthma medication such as short and long acting β -2 agonists or chromons were withheld for 24–48 h before test, as well as antihistamines for a rational period depending on the pharmacokinetic characteristics of the medication. All of the subjects participating in the study completed the spirometry and the hypertonic saline challenge procedure.

Skin prick tests

Atopic status was assessed by, SPT. They were performed on the volar aspects of the forearm with eight common standardized allergen extracts such as house dust mites (*Dermatophagoides pteronyssinus*, *D. farinae*), *Alternaria alternata*, olive tree, mixed grasses and *Parietaria officinalis* pollens, cat and dog dander, (SoluprickTM, ALK, Hørsholm, Denmark). Histamine dihydrochloride 10 mg/ml was used as positive control and 50% glycerol as negative. The response was measured as the mean diameter of the resulting wheal. The tests were considered as positive when there was at least a 3 mm mean diameter of induration after 15 min.

Statistics

SPSS statistical software program was used for data management and statistical analysis. Epidemiological and clinical characteristics were compared among groups using chi-square and one-way anova test. Correlation coefficients were done with spearman test. The two-tailed significant limit was fixed at 5%.

The study protocol was approved by, the ethics committee of Penteli Children's Hospital.

Results

The demographic data and the characteristic variables of the study groups (A, B, and C) replies to the questionnaire, baseline spirometry data as well as sensitization data are summarized in Table 1, whereas the more specific characteristics of the 20 group-A subjects are listed in Table 2.

The prevalence of asthma suggestive symptoms or other symptomatology reported from the replies to the questionnaire showed significant differences between the study groups (Table 1). Lifetime asthma symptoms were reported more frequently among group-A children (85%) than in group B (37.1%, $p = 0.001$) but not in the case of current asthma symptoms ($p = 0.35$).

At least one STP was positive in 11 of 20 (55%) children of group A, whereas the distribution of positive SPTs regarding the sensitizing allergens did not show any significant difference compared to group B (Table 1). There was no association between atopy and asthma symptoms (lifetime or current) in sIgAD group or between atopy and atopic family history in the same group.

Baseline spirometry demonstrated that FVC values in group A were lower than B and C, but the difference reached significance between A and C only ($p = 0.02$). FEV₁ values were similar in

Table 2. Characteristics of the subjects with sIgAD studied

	Name/ Sex	Date of Birth	SPT (P/S/PE)	Asthma lifetime/ current	Infection	BHR
1	SE/F	7/10/85	–	+/+	+	+
2	RP/M	21/2/90	+(S)	+/-	–	–
3	NV/M	6/5/84	+(S)	+/-	–	–
4	PI/M	4/1/88	–	+/-	–	–
5	MT/M	9/6/93	+(S)	+/-	+	–
6	PS/F	14/12/93	–	+/+	+	+
7	SI/M	24/10/83	+(S/PE)	+/-	+	–
8	PA/M	29/6/95	–	+/-	+	–
9	MA/F	23/5/91	–	+/-	–	–
10	GG/M	23/12/85	–	+/-	–	–
11	SA/F	30/5/88	+(P/S/PE)	-/-	+	–
12	SX/F	29/6/87	+(P/PE)	+/-	–	–
13	KI/M	18/2/95	–	+/-	+	–
14	PA/F	23/3/90	–	-/-	–	–
15	MP/M	10/6/90	+(S/PE)	-/-	–	–
16	PD/F	10/5/95	–	+/-	+	–
17	GV/M	4/12/95	+(P/PE)	+/+	–	+
18	DK/M	11/03/97	+(P)	+/+	–	+
19	KT/F	28/8/98	+(P)	+/+	–	+
20	FD/M	3/8/88	+(P)	+/+	+	+

SPT, skin prick testing; P, perennial allergens (mites and/or *Alternaria*); S, seasonal allergens; PE, pets; BHR, bronchial hyper-responsiveness.

all groups, with impairment of FEF₅₀ being detected in group B (Table 1).

A positive response to hypertonic saline challenge was observed in six children of group A (30%) and 25 of group B (35.7%) without any significant difference ($p = 0.8$) between the two groups. BHR was also observed in another six (5.9%) children of group C, but this prevalence was significantly lower than the prevalence of group A ($p = 0.005$) and group B ($p = 0.001$) (Fig. 1).

BHR in group-A children was observed more frequently in those who reported current asthma ($p = 0.001$) but not lifetime asthma symptoms or 'recurrent infections'. No association between atopy and BHR in the same group was found. An association to BHR was only detected among children sensitized to mites ($p = 0.03$) (Fig. 1). When children of group A with positive SPTs were compared to group B with regards to sensitizing allergen and BHR, only children of group-A sensitized to mites showed significant difference ($p = 0.002$). No relation between sensitization to pets or seasonal allergens and BHR was observed in any group (Table 3).

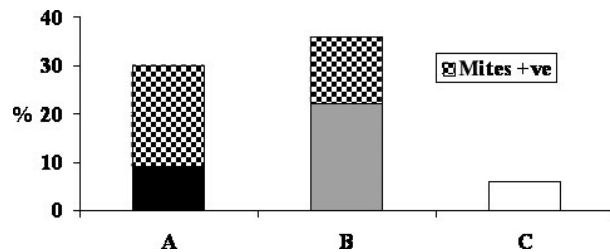


Fig. 1. Differences of prevalence of BHR among the three study groups ($p = 0.001$) and children sensitized to mites ($p = 0.03$). A, B, and C correspond to the study groups.

Table 3. Correlations of BHR with various risk factors in the three study groups

	Group A (n = 20)	Group B (n = 70)	Group C (n = 102)
BHR vs. current asthma	$p = 0.001$	$p = 0.13$	$p = 0.04$
BHR vs. lifetime asthma	$p = 0.52$	$p = 0.12$	$p = 0.08$
BHR vs. chronic rhinitis	$p = 1$	$p = 0.59$	$p = 1$
BHR vs. eczema	$p = 1$	$p = 0.50$	$p = 1$
BHR vs. sensitization to seasonal*	$p = 0.11$	$p = 0.79$	—
BHR vs. sensitization to perennial**	$p = 0.03$	$p = 0.90$	—
BHR vs. sensitization to mites	$p = 0.03$	$p = 0.83$	—
BHR vs. sensitization to <i>Alternaria</i>	—	—	—
BHR vs. sensitization to <i>alternata</i>	$p = 0.31$	$p = 0.42$	—
BHR vs. sensitization to pets	$p = 0.90$	$p = 0.58$	—

BHR, bronchial hyper-responsiveness.

*Seasonal allergens: pollen of olive tree, mixed grasses and *P. officinalis*.

**Perennial allergens: house dust mites, *A. alternata*.

Discussion

The main finding of this retrospective cohort controlled study was the association between sIgAD and the subsequent development of BHR. This association did not appear to be attributed to sIgAD *per se*, but to the sensitization to house dust mites. The prevalence of BHR was similar in both groups; in those with sIgAD (30.0%) as well as in atopics with normal serum IgA levels (35.7%), whereas it was much lower in non-sensitized with normal serum IgA (5.9%) (Fig. 1).

The study was not orientated to evaluate the prevalence of atopy in subjects with sIgAD, consequently these results do not support either the view of a more frequent sensitization of children with low levels of serum or saliva IgA as it has been reported (4, 5, 7, 11) or the opposite (5, 10). However, the prevalence of atopy in general school-age Greek population ranges from 20.5% to 29.3% (20), which is much lower compared to 55.0% found in sIgAD group.

BHR in the group of children with sIgAD was associated with sensitization to the house dust mites. Mites' exposure and sensitization is widely considered one of the most important environmental risk factor for development of BHR and asthma (21–24). sIgAD children with defective protective function in respiratory mucosa could facilitate the absorption of these potent allergens leading more easily to sensitization. Consequently, allergens, which are stronger BHR inducers, such as mites could lower the threshold of airway responsiveness in more vulnerable subjects. The fact that sensitization to house dust mites was not associated with BHR in group B might be attributed to the apparently different proportion of other sensitizing aeroallergens. On the other hand, even in children sensitized to mites other promoting mechanisms may co-exist to reach increased bronchial responsiveness (25). Thus, respiratory infection in IgA deficient children could favor BHR compared to group B.

As expected, BHR in group-A children was detected more frequently in those who reported suffering from asthma symptoms during the last 12 months, but no relation to the lifetime asthma could be ascertained, as it was reported by 85% of the children. Most of these children might in fact suffer from recurrent respiratory infections producing cough and various types of noisy breathing, recalled as 'wheezing'. There might well have been real airway narrowing, since deficient IgA protection might allow viruses to breach the mucosal defense and cause inflammation and mucosal edema in

upper as well as in lower respiratory tract. An impairment of T-cell immunity in IgA-deficient individuals increasing the susceptibility to influenza virus infection has already been reported (26). Nevertheless, it has also been reported that common respiratory infections in early childhood do not appear to be followed by persistent BHR in later childhood and early adulthood (27).

The finding that no association between atopy and asthma symptoms (current or lifetime) or atopic family history in sIgAD group was observed supports the more pivotal role of recurrent respiratory infections rather than atopy in clinical presentation of IgA deficient children. The prevalence of chronic rhinitis is unusually high (60%) and might be infectious origin, while eczema is found to be with the lowest among the three groups.

The findings of the present study do not support the Gleeson's et al. (15), as they observed an association between transient absent of IgA in saliva during infancy and the subsequent development of BHR in school age, without any correlation with current wheeze and a trend toward a negative association with atopy. However, some of the risk factors such as recurrent infections and atopic family history are not mentioned. On the other hand, 18 out of the 20 individuals with sIgAD enrolled in the present study were patients attending the outpatient clinic for their respiratory or other allergic manifestations while Gleeson's et al. (15) were recruited from a general population sample. Consequently, the two studies analyze non-comparable populations.

The lower FVC values in group A than in group B and C demonstrated by baseline spirometry most likely indicate a deficit in respiratory growth of IgA-deficient individuals. This finding could be an adverse effect of recurrent lower tract infections in the first years of life (28). However, the small number of studied patients and the extended range of their age, limits the reliability of the above observation. As expected, an impairment of FEF₅₀ was detected in the group with normal IgA and atopy. This reflects the small airways' narrowing and it could be conceivable with the fact that apart from the reported current asthma a considerable percentage of all these asymptomatic atopic children could have a silent ongoing inflammation and/or structural alterations of the airways (29).

In conclusion, these results indicate that sIgAD constitutes a risk factor for development of BHR but it appears to be related to sensitization to mites. The vulnerable mucosa facilitates recurrent

respiratory infections, which might play a crucial role in sensitization and eventually in development of BHR. Additional longitudinal research is needed to elucidate the relationship between transient as well as persistent IgA deficiency, development of sensitization and BHR.

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