



Low levels of immunoglobulin A in children with intrinsic asthma: a possible protection against atopy

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Summary Immunoglobulin A and G (IgA, IgG) serum concentrations were detected in children with nonallergic/intrinsic (36 children) or allergic/extrinsic asthma (43 children) and in age-matching control children (40 children). Asthmatic children with allergic asthma had lower IgA (1.36 ± 0.54 g/L) and higher IgG (10.48 ± 2.77 g/L) levels than the age-matching control children group (1.63 ± 0.69 vs. 9.01 ± 2.32 g/L). Children with nonallergic/intrinsic asthma had lower IgA (1.03 ± 0.41 g/L) ($p = 0.004$) and IgG (8.38 ± 1.93 g/L) ($p = 0.001$) levels than the allergic/extrinsic asthma group (1.36 ± 0.54 vs. 10.48 ± 2.77 g/L). Low IgA levels were found in children with nonallergic/intrinsic asthma and high IgG levels were found in those children with allergic/extrinsic childhood asthma.

The hypothesis is that the increased incidence of asthma in the population may be caused by a decrease in childhood infections (hygiene hypothesis). Frequent infections in early life boost the immune system, stimulating Th1-type response in young children and reducing the risk of atopic diseases.

Our hypothesis is that low IgA (and/or IgG) levels in our patients might be responsible for infection development among those children with nonallergic/intrinsic asthma. These infections stimulate the normal development of immune system in young children, reducing risk of atopy, so that those children do not get allergic/extrinsic childhood asthma.

Intrinsic childhood asthma = nonallergic (nonatopic) childhood asthma.

Extrinsic childhood asthma = allergic (atopic) childhood asthma.

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Introduction

Numerous studies suggest an increasing prevalence of childhood asthma. This trend has been ascribed to an early and increased exposure to allergens in pregnancy and during the postnatal period [1–3].

Imbalanced activation of the immunoglobulin heavy chain (IGH) genes in more hygienic environments (with a decline of infections) has also been considered in many studies [4,5].

Childhood asthma is rather specific and differs from adult asthma. Mother's history of atopy is a risk factor for asthma in the infant, and events in foetal and infant life may cause illness later in life [6,7]. Foetal and neonatal production of IL-13

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and the IL-13 gene polymorphisms seem to be important [1,8,9]. The disease development in childhood may be predicted and its course controlled by an early treatment of the atopic child (ETAC). Such measures decrease the incidence of adult asthma [10,11]. Gut-associated lymphoid tissue (GALT) can provide us with the important information the foetal and neonatal immune system since GALT is exposed to the antigens due to the swallowing of amniotic fluid and during breastfeeding [12].

The total IgE level increase in serum in children with allergic asthma is well known and is attributed to the genes that regulate basal IgE production [8,9]. The etiopathogenetic role of other immunoglobulins is controversial, as well as protective roles of IgA, IgD and IgG which have been advocated [13,14].

The aim of our study was to collect basic data about the IgA and IgG levels in the serum of children with nonallergic or allergic asthma and determine the possible correlation between infections in early childhood and the development of childhood asthma.

Methods

The study included 119 children, aged from 1 to 13.5 years old, who were admitted to the Department of Paediatrics in the University Hospital Osijek. There were 79 patients diagnosed with childhood asthma (moderate-persistent, according to GINA guidelines) [15] and 40 control subjects without respiratory symptoms. The children's parents gave their informed consent for all laboratory tests.

Asthmatic patients were divided into two groups, those with allergic childhood asthma and those with nonallergic childhood asthma. Thirty-six patients with high total IgE levels (means $\pm$ SD: 683.8 ± 394.0 KIU/L) and specific IgE antibodies

against five inhalator antigens common for eastern Croatia (Slavonia) were assigned to the allergic childhood asthma group. Forty-three patients not complying with those criteria were assigned to the nonallergic asthma group (Table 1). Children in control group without respiratory symptoms were treated in our hospital due to some other health problems (headache, obesity and abdominal pain). They had normal lung and immunological status, and the total serum IgE levels in that group was 188.8 ± 222.1 KIU/L.

Children with nonallergic asthma were younger than the allergic ones – the respective median ages were 1 year and 9 months (range 8–134 months) vs. 5 years and 1 month (range 12–137 months; $p < 0.001$). Therefore, the control group was divided into two comparable subgroups with median ages 2 years and 4 months (range 5–39 months) and 5 years and 3 months (range 31–153 months). Age differences between the matching groups were statistically insignificant.

Total IgE levels in serum (KIU/L) were measured with commercial Delfia kits (Pharmacia Diagnostics AB, Uppsala, Sweden). The concentrations of specific serum IgE antibodies (RAST) were determined according to the Phadebas radio-alergo-sorbent test (Pharmacia Diagnostics AB, Uppsala, Sweden). Immunoglobulins A, G and M in plasma were determined with radial immunodiffusion assay on Combi-RID plates (Immuno, Vienna, Austria). The results were processed using a χ^2 test, Mann–Whitney *U*-test, or ANOVA, as appropriate. The level of significance was set at $p < 0.05$.

Results

The first attacks of childhood asthma occurred significantly earlier in the nonallergic asthma group than in the allergic group of children – median ages were 10 months vs. 18 months ($p < 0.005$).

Table 1 Patients with childhood asthma and the control children with no respiratory symptoms (general data)

	Nonallergic		Allergic	
	No.	Age (months) ^a	No.	Age (months) ^a
Asthmatic patients	36 (18f/18m) ^b	21 (8–134)	43 (23f/20m)	61 (12–137) ^c
Age-matching children without respiratory symptoms	14 (9f/5m)	28 (5–39)	26 (11f/15m)	63 (31–153) ^d
Age at which asthma appeared (months)		10 (0–72)		18 (0–89) ^e
Asthma in family	6/36 (16.7%)		14/43 (32.6%)	

^aMedian and range.

^bf/m – female to male ratio.

^c $p < 0.001$ as compared to the nonallergic asthmatic patients.

^d $p < 0.001$ as compared to the nonallergic asthmatic patients.

^e $p < 0.05$ as compared to the nonallergic asthmatic patients.

Table 2 Serum IgA and IgG levels in children with allergic or nonallergic asthma

		Nonallergic	Allergic	<i>p</i>
IgA	Asthmatic patients	1.03 ± 0.41	1.36 ± 0.54	0.004
	Age-matching children without respiratory symptoms	2.08 ± 0.79	1.63 ± 0.69	0.074
	<i>p</i>	0.001	0.065	
IgG	Asthmatic patients	8.38 ± 1.93	10.48 ± 2.77	0.001
	Age-matching children without respiratory symptoms	7.15 ± 1.01	9.01 ± 2.32	0.007
	<i>p</i>	0.027	0.026	

As expected, a family history of asthma was more frequently reported in the allergic asthma group of children (14 of 43 patients, 32.6%) than in the nonallergic asthma group of children (6 of 36 patients, 16.7%) ($p \leq 0.001$). Asthmatic patients (both the allergic and nonallergic ones) had lower IgA levels than the age-matching children control group (Table 2, row 1 vs. 2). However, their IgG levels were higher (Table 2, row 3 vs. 4).

Patients assigned to the nonallergic/intrinsic asthma group had lower IgA ($p = 0.004$) and IgG ($p = 0.001$) levels than those assigned to the allergic/extrinsic group of children (Table 2, columns 1 vs. 2).

The IgM levels of all four groups were compared. Patients with childhood asthma, in nonallergic group had the values (means ± SD) of 1.93 ± 0.63 g/L and of 1.53 ± 0.59 g/L in the allergic asthma group of children. The differences between control groups were statistically insignificant according to ANOVA ($p > 0.05$).

Discussion

The hypothesis holds that the increased incidence of asthma in the population may be caused by a decrease in childhood infections, supporting our hypothesis that low IgA (and/or IgG) level in our patients may increase infection susceptibility in children with nonallergic/intrinsic childhood asthma. These infections stimulate the immune system, triggering Th1-mediated response in our children and reduce the risk for atopy.

Several authors have recently discussed the significance of antigen/allergen-specific IgA and/or IgG in asthmatic patients. Bronchoalveolar lavage fluids (BALF) in children suffering from chronic chest disease (nonallergic asthma, pneumonia and bronchitis) were reported to contain increased concentrations of IgG, IgA and IgM as compared to healthy controls [14]. Allergen-specific IgA and IgE were found in BALF, as well as in the serum of

asthmatic children [16] and adults [17,18]. High levels of IgG autoantibodies against bronchial epithelial cells were detected in adult patients with nonatopic asthma, but not in atopic patients [19]. Low levels of IgA in breast milk were associated with development of atopic eczema [20]. IgA and IgG antibodies against respiratory syncytial virus (RSV) were detected in nasal washes and serum of infants with symptoms of wheezing [21]. High titres of IgA and IgG to *Chlamydia pneumoniae* were associated with asthma morbidity [22], but another study reported the opposite finding [23], suggesting that frequent infections reduce the risk of childhood asthma among children [5]. During pregnancy, mother's immune response consists of antibody production instead of cell-mediated immunity. Foetoplacental cells secrete detectable levels of Th2 cytokines (IL-4, IL-5, IL-10 and IL-3) during all trimesters of pregnancy. Those Th2 cytokines are believed to reduce harmful effects of Th1 cytokines (IL-2, INF- γ and TNF- α) in order to protect the pregnancy [7,24].

Orofaecal infections seem to be especially important to stimulate Th1-type response of the immune system instead of Th2-type-mediated immune reactivity [25].

The low incidence of infections would allow development of Th2-type immune response at the cost of Th1-type reactivity [26,27].

Low IgA levels were found in our children with nonallergic asthma and high IgG levels in those with allergic asthma. In a similar study, Najam et al. [13] compared immunoglobulin levels in children with moderately severe asthma to the respective levels in age-matching healthy children, aged from 1 to 15 years old. IgD, IgE and IgM were higher in asthmatic children, whereas IgA and IgG levels were normal.

Our finding of increased IgG concentrations in asthmatic children corresponds with the selected literature data, but the finding of decreased IgA in our nonallergic/intrinsic asthma patients does not. However, it should be noted that we have measured total, not specific IgA and IgG levels.

Our study was affected by the age difference between the allergic and nonallergic asthma groups. Therefore, factors such as the maturity of immune system could have influenced the results. That bias was partly amended by adjusting the control groups according to the age.

One hypothesis is that during pregnancy, mother's immune response apparently consists of antibody production (like allergic), instead of cell-mediated immunity. At the same time foeto-placental cells secrete detectable levels of Th2 cytokines, similar to allergic reaction in childhood. The proposed hypothesis is that the normal functioning of immune system in childhood (Th1-type response) is highly affected by the immune stimulation (infection and low IgA) in early childhood. If there is no immune system stimulation due to infection (low IgA), then the Th2-type-mediated immune reactivity (like during pregnancy) would persist and prevail. This could be the main reason for increased incidence of allergic disease in the population today.

The proposed hypothesis. Infection decline in early childhood is responsible for rare Th1-type response of immune system and more Th2-type-mediated immune reactivity. After childbirth, the immune stimulation due to infection (low concentrations of IgA) might protect against atopic diseases in childhood and later in adult life. Natural environment teeming in early childhood with infections (e.g., low concentrations of IgA) during childhood is convenient and would stimulate normal, immune Th1-type-mediated reactivity unlike the immune reaction in pregnancy (similar to allergic).

Based on our results, we suppose that low levels of IgA in our patients (with nonallergic/intrinsic asthma) may be responsible for frequent infections. Nevertheless, the infections, in turn, could positively stimulate the immune system (Th1-type cytokines response), promote its acquisition of competence and prevent atopy, meaning that low IgA levels may be a protective factor in etio-pathogenesis of our patients with nonallergic/intrinsic childhood asthma.

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