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Selective IgA deficiency in early life: Association to infections and allergic diseases during childhood[☆]

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KEYWORDS

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Abstract Selective IgA deficiency in early life is quite common in Caucasian populations, but it is unclear whether it increases the risk of infections and allergic diseases during childhood. Serum IgA levels were measured in 2423 children at 4 years of age in a Swedish population based birth cohort (BAMSE). Parental questionnaires were repeatedly sent out during the child's first 8 years of life, collecting information about infections and allergic diseases. 14 children (1:173) were found to be IgA deficient at 4 years of age. These children had an increased risk of pseudocroup at year 1 ($p < 0.01$) and food hypersensitivity at year 4 ($p < 0.05$) as compared to IgA sufficient children. No increased risk was observed in the partial IgA deficiency group. The findings suggest that selective IgA deficiency may increase the risk of parentally reported pseudocroup and food hypersensitivity during early childhood.

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Abbreviations: BAMSE, Children, Allergy, Milieu, Stockholm, Epidemiological survey; CI, Confidence interval; ELISA, Enzyme-Linked ImmunoSorbent Assay; IgA, Immunoglobulin A; IgAD, Selective IgA deficiency; IgE, Immunoglobulin E; IgG, Immunoglobulin G; PBS, Phosphate-buffered saline.

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Introduction

Selective IgA deficiency (IgAD) is the most common primary immunodeficiency disorder in Sweden with an estimated prevalence of 1:600 [1]. The prevalence ranges from 1:328 in American blood donors [2] to 1:18 550 in Japanese blood donors [3]. The current definition, established by the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiencies, defines IgAD as serum IgA levels below 0.07 g/l with normal IgM and IgG levels in individuals of 4 years of age or older [4] (www.esid.org). Children below 4 years of age have a poorly developed IgA secretory system, thus making a diagnosis of IgAD difficult. The disorder is caused by a defect at the stem cell level, as shown by transfer of the deficiency after bone marrow transplantation from an IgA deficient donor to a recipient with previously normal IgA levels [5]. Moreover, bone marrow transplantation from a normal donor to an IgAD recipient resulted in normal serum IgA levels in the recipient [6].

The prevalence of IgAD in healthy adults, primarily blood donors, has been extensively studied [1], providing a firm foundation for further investigations. The frequencies obtained in adult populations should, however, not automatically be extrapolated to children and adolescents, as serum IgA does not reach adult levels until the early teens. The existing prevalence figures in studies on healthy children [7–19] are summarized in Table 1 and the reported figures range from 1:90 in the Netherlands [7] to 1:2095 in Tunisia [19]. As IgAD is seen in approximately 1 in 600 in the adult Swedish population [1], it suggests that the disorder may be more common in children, possibly due to a not yet fully developed immune system.

A majority of the affected individuals are asymptomatic, but one third of the adult patients suffer from recurrent infections of the upper respiratory tract, gastrointestinal disorders, autoimmune disorders, and possibly allergic diseases [20,21]. The infections are often viral and clinically mild to moderate, while bacterial infections are relatively uncommon [22]. Gastrointestinal diseases include giardiasis, nodular lymphoid hyperplasia, celiac disease, and inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Autoimmune disorders are also frequently seen in

IgAD patients and include rheumatoid arthritis, systemic lupus erythematosus, haemolytic anaemia, thyroiditis, diabetes type I, pernicious anaemia, dermatomyositis, chronic active hepatitis, Addison's disease, Sjögren's syndrome, and idiopathic thrombocytopenic purpura [22,23].

An increased frequency of allergic manifestations in IgAD patients has been previously reported [24,25]. Buckley and Dees reported that 14 out of 24 patients (children and adults) with IgAD had atopic diagnoses (58%) [24], though no definition of atopy was given. In 2008, Aghamohammadi et al. reported that 19 out of 23 (83%) IgAD patients, aged 4–32 years, suffered from allergic diseases including asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, urticaria, drug allergy or food allergy [25]. In 2004, 39% of the children and 30% of the adults in the general population in UK, were diagnosed with one or more atopic condition (allergic rhinitis, anaphylaxis, asthma, conjunctivitis, eczema/dermatitis, food allergy and urticaria/angioedema) [26]. The allergic diseases most commonly associated with IgAD are rhinoconjunctivitis, urticaria, atopic eczema and bronchial asthma [23]. However, the findings are not conclusive, as some studies show no increased frequency of allergies in IgAD subjects [27–31].

Because of the known increased incidence of autoimmune disorders and, although disputed, allergic diseases, in IgAD patients [20,21], it is of importance to obtain a better understanding of the pathophysiology associated with IgAD in children. The aim of this study was to determine the prevalence of IgAD and partial IgAD (0.07–0.49 g/l) in Swedish children and to investigate the relation to allergic diseases and infections during childhood. Determination of serum IgA levels was performed using ELISA and serum microarrays [32], the latter being a high-throughput platform for semi-quantitative determination of concentrations of serum proteins.

Methods

Patient samples

During 1994–1996, all newborns in a predefined area of Stockholm were invited to participate in a prospective

Table 1 Prevalence of IgA deficiency among non-hospitalized children during 1969–2007 (<20 years).

Year	Ref	Country	Sample size	Age in years	Prevalence	Criteria (g/l)	Type of population ^a
1969	[7]	Netherlands	270	4–13	1:90	<0.05	CS
1969	[8]	Sweden	219	2–15	1:219	<0.01	HC
1972	[9]	Canada	2170	5–19	1:310	<0.04	CS
1975	[10]	USA	535	4–17	1:268	<0.01	CS
1982	[11]	Canada	694	NM	1:347	<0.05	HC
1984	[12]	Nigeria	161	1–15	0	NM	HC
1988	[13]	Nigeria	1639	5–15	1:137	<0.05	HC
1988	[14]	Israel	79	5–16	0	NM	HC
1997	[15]	Spain	1856	2–16	1:169	<0.07	CS
1997	[16]	Italy	988	1–15	0	<0.05	HC
2003	[17]	Brazil	2034	1–14	1:509	<0.05	CS
2005	[18]	Turkey	1263	6–17	0	NM	CS
2007	[19]	Tunisia	6286	9.66±2.73 ^b	1:2095	<0.05	CS
Present study		Sweden	2423	4	1:173	<0.07	CS

^a CS=community study. HC=healthy controls. NM=not mentioned.

^b Mean±2 SD.

study (the Children, Allergy, Milieu, Stockholm, Epidemiological survey [BAMSE]) and 75% of all the children born in this area were included ($N=4089$). Among parents to non-responders and actively excluded children, smoking when the child was 2 months old was less common as compared to parents to children in the study group, but in other background factors of importance, no significant differences were found. The details of the study design have been described elsewhere [33]. Data on parental allergy and various exposures were collected using a questionnaire when the children were 2 months old in average. At 1, 2, 4 and 8 years of age, the questionnaires focused on the children's allergic symptoms and possible confounding factors. All children who answered the questionnaires at 4 years of age ($n=3670$) were asked for a blood sample and altogether 2614 samples (71%) were collected. After excluding those with low amounts of serum (low sample volume at collection), 2423 samples (66%) from the 4-year follow-up were included in the present study. In addition, serum samples collected at the 8-year follow-up from the individuals lacking IgA at 4 years of age were tested using sandwich ELISA ($n=10$). Ethical approval was obtained from the local ethical review board in Stockholm.

ELISA

Total serum IgA levels were determined by sandwich ELISA using polyclonal rabbit anti-human IgA antibodies (DAKO, Denmark) and alkaline phosphatase-conjugated rabbit anti-human serum IgA antibodies (Jackson ImmunoResearch Laboratories, USA). Polystyrene plates (Corning Incorporated, USA) were coated over night at room temperature with 100 μ l per well of the primary antibody (1.2 mg/l) diluted in carbonate bicarbonate buffer (0.05 M). The plates were washed four times with phosphate-buffered saline (PBS) with 0.5% Tween20 between the incubations. The samples were three-fold serially diluted in PBS with 0.5% Tween20. All samples were titrated against a six-fold serially diluted standard, ranging from 3.125 μ g/l to 100 μ g/l. The samples, the standard dilutions and a blank (PBS with 0.5% Tween20) were added in duplicate and incubated over night at room temperature. The alkaline phosphatase-conjugated antibodies were added (0.6 mg/l) and incubated for 2 h at room temperature. p-Nitrophenyl phosphate (Sigma-Aldrich, USA) was added and the absorbance (405 nm) was read on a Vmax microplate reader (Molecular Devices, USA). A mean concentration was obtained for each sample using Deltasoft JV 1.8 (Biometallics Inc, USA). Samples with IgA levels of 0.3 g/l or lower ($n=28$) were retested on ELISA. Re-testing was also carried out for 100 samples with the highest discrepancy in IgA levels between ELISA and microarrays. No new deficiencies were identified and all 14 previously found deficiencies were confirmed.

In addition, total serum IgG levels were determined in the individuals with IgA deficiency using sandwich ELISA. Polyclonal rabbit anti-human IgG antibodies (DAKO, Denmark) and alkaline phosphatase-conjugated polyclonal rabbit anti-human IgG antibodies (DAKO, Denmark) were added at a concentration of 0.6 mg/l and 1.1 mg/l respectively. The same protocol as for determination of serum IgA was followed.

Serum microarrays

The serum samples were diluted 1:10 PBS with 0.5% Tween20, loaded onto 384 well plates in volumes of 30 μ l/well (Genetix, UK) and printed in duplicate (in 14 identical blocks) on Corning Epoxide slides (Corning Incorporated, USA) using a non-contact printing robot (Nano-plotter 2.0, Gesim, Germany). The slides were incubated in a humidity box (75%) for 16 h at room temperature and blocked with SuperBlock solution (Pierce Biotechnology, USA) using an air-brush pistol. Polyclonal rabbit anti-human IgA antibodies (DAKO, Denmark) were added at a concentration of 46 μ g/l. Alexa Fluor 555 goat-anti-rabbit IgG (Molecular Probes, USA) was used as a secondary antibody at a concentration of 33 μ g/l. The slides were scanned in a G2565BA array scanner (Agilent, USA) with the photo multiplier tube set to 100% for both channels and scan resolution 10 μ m.

The resulting images were analyzed with GenePix-Pro 5.1 (Axon Instruments, USA) using non-circular feature alignment. An inter-slide normalization was performed to correct for incubation artifacts. The median intensity of each spot was averaged based on replicates and the correlation between the microarrays and ELISA was calculated using R console (www.r-project.org).

Definition of health outcomes

Data on environmental factors including maternal age, maternal smoking habits, breast-feeding and parental allergies were collected from parent-answered questionnaires when the children were on average 2 months old. Questions regarding symptoms related to allergic diseases and infections in their children were answered by the parents at years 1, 2, 4 and 8.

Pseudocroup, pneumonia, bronchitis and respiratory syncytial virus infection were parent reported and defined as doctor's diagnosis during the 12 months prior to answering the questionnaire. Parentally reported pseudocroup is defined as a sudden spasm of the larynx that occurs in children and is marked by difficult breathing with prolonged noisy inspiration, normally caused by viral infection. *Parentally reported asthma* at years 1 and 2 was defined as at least 3 episodes of wheezing in combination with treatment with inhaled steroids or signs of hyperactivity [34]. At 4 and 8 years of age the definition included at least 4 episodes of wheezing in the last 12 months or at least 1 episode of wheezing combined with inhaled steroids treatment [35]. *Parentally reported eczema* was defined as dry skin and itchy rash continuously for at least 2 weeks in the previous 12 months with a typical distribution (face, outer limbs, folds of elbows/wrists, behind the knees, or fronts of ankles) and/or doctor's diagnosis [36]. *Parentally reported wheeze* was defined as at least 1 episode of wheezing in the last 12 months. *Sensitization to inhalant allergens* was defined as positive Phadiatop® (IgE-antibody levels ≥ 0.35 kU_A/l) against cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, or *Cladosporium* species.

Sensitization to food allergens was defined as positive fx5® (IgE-antibody levels ≥ 0.3 kU_A/l) against cow's milk, hen's egg, codfish, soybean, peanut or wheat.

Parentally reported food hypersensitivity was defined as parentally reported symptoms (wheeze, itchy eyes and/

Table 2 Descriptive data for the study population ($n=2423$) in relation to serum IgA levels.

	Study population ($n=2423$)	
	<0.07 g/l n (%)	>0.07 g/l n (%)
Total number of children	14	2409
Age at investigation (months)	52	52
Sex (male)	6 (43)	1224 (51)
Maternal age (<25)	1 (7)	184 (8)
Parental history of allergic disease ^a	4 (29)	734 (31)
Breast-feeding (>4 months)	12 (86)	1903 (80)
Maternal smoking ^b	2 (14)	311 (13)

^a Physician's diagnosis of asthma, hay fever, or both in a parent combined with allergy to furry pet or pollen.

^b Maternal smoking during pregnancy or at enrolment.

or running nose, facial oedema, urticaria, eczema or vomiting/diarrhoea) related to ingestion of a certain food [37].

Statistical analyses

At 4 years of age, the normal serum IgA levels are 0.5–2.3 g/l (reference values at the Laboratory of Clinical Immunology, Karolinska Hospital, Stockholm). Children with IgA levels ranging from 0.07 to 0.49 g/l were thus regarded as partially deficient. For the association analysis, the children were categorized into three groups: 1) serum IgA levels less than 0.07 g/l; 2) serum IgA levels ranging from 0.07 to 0.49 g/l; and 3) serum IgA levels of 0.5 g/l and above. Analyses to establish whether the partially deficient group of children ($n=328$) differs in any respect from the group with normal IgA levels ($n=2081$) were also performed. Differences in the distribution of selected characteristics and association with selected outcomes were tested using χ^2 test and $p<0.05$ was regarded as significant. All statistical analyses were performed with Stata 9.0 (College Station, TX, USA).

Results

To determine the prevalence of IgAD in Swedish children, IgA levels were measured in 2423 serum samples using serum microarrays and sandwich ELISA.

Serum microarrays enable simultaneous analysis of thousands of samples and are suitable for high-throughput analysis. This platform generally generates semi-quantitative data but is not perfectly suited for absolute measurements. However, it is highly applicable to initial screening procedures for relative measurements of medium and highly abundant proteins in complex samples. The two methods were used simultaneously to investigate whether the IgAD samples identified by traditional ELISA were also identified by the serum microarrays.

14 children with IgAD (<0.07 g/l) were identified using ELISA, giving a prevalence of 0.6%, which corresponds to one in 173. The fluorescent signals in the IgAD group (mean signal strength of 1600) were significantly lower ($p<0.01$) than in the remaining sample set (mean signal strength 9600) when using serum microarrays. All 14 subjects had normal serum levels of IgG (data not shown).

Table 3 History of infection-related diseases during the first 8 years of life in IgA deficient and non-IgA deficient children.

	<0.07 g/l n (%)	>0.07 g/l n (%)	p -value
Total number of children	14	2409	
Pseudocroup ^a year 1	3 (21)	123 (5)	0.007
Pseudocroup ^a year 1 and/or 2	4 (29)	264 (11)	0.04
Pseudocroup ^a year 4	2 (14)	244 (10)	0.61
Pneumonia ^a year 1 and/or 2	1 (7)	187 (8)	0.93
Pneumonia ^a year 4	0 (0)	127 (5)	0.38
Bronchitis ^a year 1 and/or 2	2 (14)	365 (15)	0.93
Bronchitis ^a year 4	2 (14)	248 (10)	0.63
Antibiotics year 1 and/or 2	12 (86)	1732 (72)	0.24
Antibiotics year 4	12 (86)	1743 (73)	0.27
Antibiotics year 8	13 (100)	1987 (88)	0.18
RS virus ^b	0 (0)	98 (4)	0.44
Otitis year 1	2 (14)	547 (23)	0.44
Infections ^c years 1, 2 and/or 4	7 (50)	899 (37)	0.32

^a Physician's diagnosis.

^b Respiratory syncytial virus.

^c One or more of the following at 1,2 and/or 4 years: pseudocroup, pneumonia, bronchitis.

Table 4 Association between IgA levels at 4 years of age and allergic diseases at 1 to 8 years of age.

	<0.07 g/l n (%)	>0.07 g/l n (%)	p-value
Total number of children	14	2409	
Asthma ^a at year 1 and/or 2	1 (7)	197 (8)	0.89
Asthma at year 4	1 (7)	179 (8)	0.96
Asthma at year 8	1 (8)	142 (6)	0.83
Eczema ^b at year 1 and/or 2	2 (15)	622 (26)	0.37
Eczema at year 4	3 (21)	499 (21)	0.95
Eczema at year 8	2 (17)	409 (18)	0.88
Wheeze ^c at year 1 and/or 2	3 (21)	635 (26)	0.68
Wheeze at year 4	3 (21)	372 (16)	0.54
Wheeze at year 8	1 (8)	237 (11)	0.74
Sensitization ^d at year 4	4 (29)	561 (23)	0.64
Sensitization at year 8	4 (40)	640 (34)	0.71
Sensitization to food allergens ^e at year 4	3 (21)	365 (15)	0.51
Sensitization to food allergens at year 8	3 (30)	358 (19)	0.39
Sensitization to inhalant allergens ^f at year 4	1 (7)	352 (15)	0.43
Sensitization to inhalant allergens at year 8	3 (30)	477 (26)	0.75
Food hypersensitivity ^g at year 1	2 (14)	233 (10)	0.59
Food hypersensitivity at year 2	2 (15)	228 (10)	0.49
Food hypersensitivity at year 4	4 (33)	255 (12)	0.02
Food hypersensitivity at year 8	4 (31)	283 (13)	0.05
Any "allergy" ^h at year 1,2 and/or 4	6 (43)	1392 (58)	0.27

^a According to definition: symptoms and treatment.^b Physician's diagnosis.^c At least one wheezing episode in the last 12 months.^d IgE-value for food mix and/or Phadiatop >0.35 kU_A/l.^e IgE-value for food mix >0.35 kU_A/l.^f IgE-value for Phadiatop >0.35 kU_A/l.^g One specific food item and one specific symptom reported.^h One or more of the following at 1,2 and/or 4 years: asthma, eczema, wheeze, food hypersensitivity.

The basic characteristics of the study population in relation to serum IgA levels are given in Table 2. None of the characteristics differed significantly between the deficient and non-deficient groups. Children having IgAD had a significantly increased risk of parentally reported pseudocroup at year 1 ($p < 0.01$) and pseudocroup at 1 and/or 2 years of age ($p < 0.05$) compared to non-deficient children (Table 3). No significant association was seen for pneumonia

or bronchitis at any age. For allergic diseases, IgAD children were found to have a significantly increased risk of parentally reported food hypersensitivity at 4 years of age ($p < 0.05$). At 8 years of age there was a tendency to increased risk for food hypersensitivity ($p = 0.05$) (Table 4). No significant association was seen for asthma, eczema or sensitization (IgE) at any age. The health outcomes did not differ significantly between children with partial IgA

Table 5 Health outcomes in ten children with transient and sustained IgAD.

Subject	Serum IgA at 4 years	Serum IgA at 8 years	Allergies/infections
1.	<0.07 g/l	1.3 g/l	Sensitization to food and inhalant allergens year 8.
2.	<0.07 g/l	0.3 g/l	Pseudocroup years 1, 2, 4.
3.	<0.07 g/l	0.3 g/l	Sensitization to food allergens year 4, 8. Pseudocroup year 1.
4.	<0.07 g/l	0.2 g/l	–
5.	<0.07 g/l	0.2 g/l	Food hypersensitivity years 2, 4, 8. Sensitization to inhalant allergens year 8. Wheeze, pseudocroup, bronchitis year 1.
6.	<0.07 g/l	<0.07 g/l	Asthma years 1,2,4,8. Eczema years 1, 2, 4 ^a . Food hypersensitivity years 1, 8. Sensitization to inhalant allergens years 4, 8. Sensitization to food allergens year 8. Bronchitis year 4.
7.	<0.07 g/l	<0.07 g/l	Sensitization to food allergens year 4 ^b . Pseudocroup year 2.
8.	<0.07 g/l	<0.07 g/l	Wheeze year 4.
9.	<0.07 g/l	<0.07 g/l	–
10.	<0.07 g/l	<0.07 g/l	Eczema and food hypersensitivity years 1, 2, 4, 8.

^a Data on eczema at 8 missing.^b Food hypersensitivity data at 4 missing.

deficiency ($n=328$) (0.07–0.49 g/l) and those with normal serum IgA levels (Supplementary Tables 1 and 2).

Ten of the 14 deficient children had serum samples available from the 8-year follow-up. The serum IgA levels in these samples were tested using ELISA and 5 out of 10 children were still IgA deficient (<0.07 g/l). Out of the remaining five, one child showed normal IgA levels (1.3 g/l), while four were partially deficient (Table 5). Assuming that the remaining 4 children were distributed equally, i.e., that 50% remained IgA deficient, 7 out of 14 children would be expected to be IgAD at 8 years of age, giving a prevalence of 1:347.

Discussion

This survey of 2423 Swedish children from the BAMSE cohort revealed 14 subjects with IgAD at 4 years of age, giving a prevalence of 0.6% (1:173). When compared to a prevalence of approximately 1:600 in the general adult population in Sweden [1], it might suggest a dynamic process with IgAD being more common among children due to their yet not fully mature IgA synthesis system, but an actual increase in prevalence cannot be ruled out. A majority of paediatric studies report a prevalence of 1:90–1:509, which is in line with our findings. Due to differences in the definition of IgAD, such as age of the subjects and the cut-off for serum IgA levels, it is, however, difficult to compare the results from the different studies. In a majority of the paediatric studies, the age range of the children is broad and often no information is available regarding the distribution.

The microarray platform is suitable for detection of specific proteins in thousands of samples simultaneously. Previously, we reported very good correlation between sandwich ELISA and serum microarrays for IgA levels in 2009 serum samples from adult individuals [32]. The method has also been used for successful determination of C3 levels in dried blood spot samples collected at birth [38]. As the 14 samples lacking serum IgA were also showing the lowest intensities on serum microarrays, it would be theoretically possible to screen thousands of samples and subsequently determine serum IgA levels in those with the lowest intensity using ELISA in order to identify individuals with IgAD. As many patients with different forms of antibody deficiencies lack IgA, a screening could theoretically be used for identification of individual with various humoral deficiencies. Although the screening would result in identification of individuals with partial IgAD, it seems to be clinically irrelevant, as the present findings suggest no significant difference in clinical findings when compared to children with normal levels of serum IgA.

The health outcomes significantly associated with IgAD in our study include pseudocroup at year 1 and food hypersensitivity at 4 years of age. At year 1, 3 out of 14 deficient children have reported pseudocroup, compared to 123 out of 2409 in the non-deficient group. As the significance is seen during early childhood, we believe that it strengthens the assumed infectious aetiology in these children. Alternatively, the IgAD children may be more prone to developing pseudocroup as a result of respiratory infections without a general increase in susceptibility. Pseudocroup is caused by viral infections (mainly parainfluenzae) while e.g. pneumonia and otitis are mainly caused by bacterial infections.

A possible cause for the significant findings at year 1 but not later is that of compensatory mechanisms. Age-related compensatory mechanisms have previously been reported in patients with other forms of primary immunodeficiency disorders, such as C3 deficiency [39,40] where individuals prone to infections during childhood became symptom-free adults. The fact that pseudocroup at 1 and/or 2 years of age is significant strengthens the finding of increased risk in early childhood. The combined analysis at 1 and/or 2 years of age also increased the number of affected children and correspondingly the power.

Symptoms from the GI tract are a common feature in symptomatic IgAD patients. Therefore, we believed that allergic manifestations of the GI tract would be predominant. Other allergy-related variables were chosen on the basis of previously reported associations. The significantly increased risk of food hypersensitivity might indicate an association between IgAD and allergic manifestation in the GI tract. Furthermore, there is a trend of increased risk for food hypersensitivity at all ages, thus strengthening the assumption of a real association. As we did not find any association between IgAD and increased levels of specific IgE, it suggests that the increased risk for food hypersensitivity in IgAD children is not IgE-mediated.

It is important to point out that the lack of association to other infection- or allergy-related health outcomes does not necessarily exclude an association, due to the small number of deficient children. The study nevertheless yielded significant results, suggesting that the associations are of clinical relevance.

When comparing children with partial IgAD to those with normal IgA levels, we noted no significant differences, suggesting that the impaired health outcomes identified in this study are limited to children with a total lack of serum IgA.

An increased frequency of allergic diseases has previously been reported in IgAD patients [24,25] while other studies [27–31] show no increased frequencies of allergic diseases compared to the general population [26]. It should be noted that allergies are clinically heterogeneous and may have different underlying mechanisms depending on factors such as heredity and age [41]. It is thus possible that transient IgAD may predispose children to allergies during certain periods of time, as suggested by several studies [42,43]. The fact that food hypersensitivity in this study is parentally reported is a possible limitation of this study. However, similar definitions have been used in other population based studies [37,44–46] and there still is a statistically significant difference in prevalence of parentally reported food hypersensitivity between children with, and without IgAD.

Many studies have shown that a fair proportion of the paediatric IgAD cases are transient [11,47–54]. A study on normalization of IgA levels in deficient children showed that 6 out of 18 subjects with total IgAD normalized their IgA levels with time [47]. In contrast, Plebani et al., reported that out of 40 children with total IgAD, none had reached normal serum IgA levels at follow-up 1.5 to 9 years later [54], nor had any of the 36 children with total IgAD that were followed up 5 years later by de Laat et al. [52]. Among the ten IgAD children with serum samples available at 8 years of age, we only found one subject with a normalized IgA level, while four remained partially deficient.

In conclusion, the present study is one of the largest paediatric IgAD prevalence studies in the world. Moreover, extensive data have been collected for each individual with focus on allergies and infections during childhood, thus resulting in one of the best described cohorts for allergy studies. We show that the prevalence of IgAD in Swedish children at 4 years of age is higher than in adults. Children with IgAD at 4 years of age seem to have an increased risk of pseudocroup early in life and may be at a higher risk of having concurrent allergic manifestations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.clim.2009.05.014](https://doi.org/10.1016/j.clim.2009.05.014).

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Supplementary table I. History of infection-related diseases during the first 8 years of life in 2409 children with partial IgAD and with normal serum IgA levels.

	0.07-0.49 g/l n (%)	≥0.50 g/l n (%)	P-value
Total number of children	328	2081	
Pseudocroup ² year 1	16 (5)	107 (5)	0.83
Pseudocroup ² year 1 and/or 2	33 (10)	231 (11)	0.59
Pseudocroup ² year 4	30 (9)	214 (10)	0.52
Pneumonia ² year 1 and/or 2	21 (6)	166 (8)	0.33
Pneumonia ² yr 4	18 (5)	109 (5)	0.85
Bronchitis ² yr 1 and/or 2	51 (16)	314 (15)	0.81
Bronchitis ² yr 4	38 (12)	210 (10)	0.42
Antibiotics yr 1 and/or 2	241 (73)	1491 (71)	0.43
Antibiotics yr 4	238 (73)	1505 (73)	0.87
Antibiotics yr 8	272 (90)	1715 (88)	0.32
RS virus ³	8 (2)	90 (4)	0.11
Otitis yr 1	72 (22)	475 (23)	0.72

¹Adjusted for age at blood collection at the 4-year follow up. ²Physician's diagnosis. ³Respiratory syncytial virus.

Supplementary table II. Association between IgA levels at 4 years of age and allergic diseases at 1 to 8 years of age in 2409 children with partial IgAD and with normal serum IgA levels.

	0.07-0.49 g/l n (%)	≥0.50 g/l n (%)	P-value
Total number of children	328	2081	
Asthma ² at year 1 and/or 2	26 (8)	171 (8)	0.87
Asthma at year 4	28 (9)	151 (7)	0.41
Asthma at year 8	20 (7)	12 (6)	0.85
Eczema ³ at year 1 and/or 2	87 (27)	535 (26)	0.77
Eczema at year 4	65 (20)	434 (21)	0.67
Eczema at year 8	47 (16)	362 (19)	0.18
Wheeze ⁴ at year 1 and/or 2	88 (27)	547 (29)	0.81
Wheeze at year 4	46 (14)	326 (16)	0.43
Wheeze at year 8	30 (10)	207 (11)	0.67
Sensitization ⁵ at year 4	69 (21)	492 (24)	0.32
Sensitization at year 8	81 (32)	559 (35)	0.47
Sensitization to food allergens ⁶ at year 4	42 (13)	323 (15)	0.21
Sensitization to food allergens at year 8	47 (19)	311 (19)	0.85
Sensitization to inhalent allergens ⁷ at year 4	38 (12)	314 (15)	0.10
Sensitization to inhalent allergens at year 8	56 (22)	421 (26)	0.21
Food hypersensitivity ⁸ at year 1	29 (9)	204 (10)	0.54
Food hypersensitivity at year 2	32 (10)	196 (10)	0.88
Food hypersensitivity at year 4	34 (11)	221 (12)	0.86
Food hypersensitivity at year 8	34 (11)	249 (13)	0.43

¹Adjusted for age at blood collection at the 4-year follow up. ²According to definition: symptoms and treatment. ³Physician's diagnosis. ⁴At least one wheeze episode in the last 12 months. ⁵IgE-value for food mix and/or phadiatop ≥ 0.35 kU/l. ⁶IgE-value for food mix ≥ 0.35 kU/l. ⁷IgE-value for phadiatop ≥ 0.35 kU/l. ⁸One specific food item and one specific symptom reported.