

Original Article

Asthma and allergic symptoms and type 1 diabetes-related autoantibodies in 2.5-yr-old children

Wahlberg J, Vaarala O, Ludvigsson J, for the ABIS Study Group. Asthma and allergic symptoms and type 1 diabetes-related autoantibodies in 2.5-yr-old children.
Pediatric Diabetes 2011.

A dominance of Th2 cytokine pattern is associated with allergic diseases, whereas a Th1 pattern has been reported in autoimmune type 1 diabetes (T1D). The Th1/Th2 paradigm has led to the interest in the relationship between these diseases. To investigate the association between atopic diseases, asthma and occurrence of T1D-related β -cell autoantibodies in children, we studied 7208 unselected 2.5-yr-old children from the All Babies in Southeast Sweden (ABIS) cohort. The ABIS cohort includes 17 055 (78.3% out of all 21 700) children born from October 1997 to October 1999, and followed prospectively with regular biological samples and questionnaires, at birth, at 1 and 2.5 yr. Risk factors for development of β -cell autoantibodies at the age of 2.5 yr were type of domiciliary, domestic animals (cat and dog) and getting a new brother/sister during first year of life. Maternal smoking during pregnancy [odds ratio (OR) 1.6] and heavy smoking at home (>10 vs. ≤ 10 cigarettes) implied risk for tyrosine phosphatase autoantibodies (IA-2A) (OR 2.9). Wheezing during the first year of life implied risk for glutamic acid decarboxylase autoantibodies (GADA) (OR 1.9) and double positivity for GADA and IA-2A (OR 9.1). Rash on several locations (at least three times during 12 months) (OR 1.7) as well as allergic symptoms related to fur-bearing animals (OR 2.7) implied risk for IA-2A. Food allergy against egg, cow-milk, fish, nuts/almonds (one or in combination) implied risk for GADA and IA-2A (OR 4.5). In a regression model wheezing during first year of life remained as a risk factor for GADA [OR 2.0, confidence interval (CI) 1.1–3.8; $p = 0.031$] and both GADA and IA-2A (OR 10.7, CI 3.9–29.4; $p = 0.000$). We conclude that allergic symptoms are associated with the development of T1D-related autoantibodies during the first years of life.

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Key words: asthma – allergy – GADA – IA-2A – T1D

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Submitted 15 April 2010. Accepted for publication 5 January 2011

As early as in the 1930s, several studies indicated that people with diabetes had asthma less often than had the control subjects, and vice versa (early studies summarized by Helander) (1). Not all of these early studies were entirely consistent, and many had methodological weaknesses, such as no or improper control groups, or probable inclusion of type 2 diabetes (T2D).

The explanations of the apparent inverse relationship have been obscure. The reciprocal control of Th1/Th2 immune responses has again evoked the interest in

the relationship between atopic diseases and type 1 diabetes (T1D).

A Th2 cytokine pattern is typically seen in allergic immunoglobulin E (IgE)-mediated responses, whereas a Th1 cytokine pattern has been reported in the islets in autoimmune T1D. The Th2 associated cytokines, such as interleukin (IL)-4 and IL-13, tend to inhibit the Th1 responses and Th1-associated interferon-gamma down-regulates Th2 responses.

It is probable that there are differences in the genetic background predisposing to asthma, atopic dermatitis,

and T1D (2). However, shared candidate genetic markers have also been implicated in T1D and atopic eczema, although not conclusively, including polymorphisms in the region encoding IL-4 receptor α -unit.

The hygiene hypothesis argues that early environmental stimulation by infections is necessary to achieve a mature and balanced repertoire of immune responses (3). The incidence of childhood T1D has risen in parallel with that of childhood asthma and atopic diseases. The hygiene hypothesis has been proposed to explain the parallel increase of T1D and atopic diseases because of reduced stimulation of the immune system by early infections (4). The risk of allergic diseases has been reported to be inversely correlated with infections, such as hepatitis A, in epidemiological studies (5). Studies in T1D are more indirect, but the incidence of autoimmune diabetes in animal model is modified by microbial exposure (6). The protective effect induced by microbial load balancing immune responses is probably mediated by regulatory T lymphocytes. Co-evolutionary partners might have contributed to the development of this form of response, and parasites and the indigenous biota of the gut are plausible candidates.

T1D is preceded by the appearance of circulating islet autoantibodies that can be used for assessing diabetes risk in non-diabetic individuals (7). Glutamic acid decarboxylase autoantibodies (GADA) and the protein tyrosine phosphatase-like antigen IA-2 (IA-2A) are two of the best established markers of progression to diabetes. The risk for developing diabetes is related to multiple autoantibody responses, i.e., prediction increases with the positivity of two or more autoantibodies (8, 9).

On the basis of this discussion, we studied the association of early symptoms and known environmental risk factors of atopic diseases with the occurrence of β -cell autoimmunity at the age of 2.5 yr in a non-selected population-based cohort of Swedish children.

Materials and methods

All Babies in Southeast of Sweden (ABIS) is a population based cohort study in which newborns have been followed prospectively with regular biological samples and questionnaires.

The infants were born between October 1997 and October 1999 in Southeast of Sweden. Twenty one thousand seven hundred newborns and their families were asked and 17 055 newborns (78.6%) participated in the ABIS study. Informed consent was obtained from the parents before enrollment. The ABIS population is representative for the general Swedish population (10).

Lysed whole blood samples taken at 2.5 yr of age were stored at -20°C until analyzed. Among the ABIS

population a random sample of 7208 children aged 2.5-yr was used for the present study on association of atopic diseases, asthma, and occurrence of β -cell autoantibodies related to T1D.

The Research Ethics Committees at the Faculty of Health Sciences, Linköping University and at the Medical Faculty, Lund University, Sweden, approved the project.

GADA and IA-2A were determined by an immune precipitation method using methionin-labelled antigens. The method is described in detail elsewhere (11). Positivity for IA-2A and GADA was determined as antibody levels above the 95th percentile for 2.5-yr-old healthy children, which corresponds to 26 RA units (26.3 WHO units) for IA-2A and 82.2 RA units (27.5 WHO units) for GADA. In the second international workshop (Diabetes Autoantibody Standardisation Program, 2003) the specificity was 100% for IA-2A and 98% for GADA assay and the sensitivity was 50% and 78%, respectively. Intra-assay coefficient of variation was 5.2% and inter-assay variation 13–18%.

Questionnaires were completed at birth, age 1, and 2.5 yr. In the questionnaires, parents were asked for factors related to asthma and allergy. These questions were assessed from the International study of asthma and allergies in childhood (ISAAC) protocol. ISAAC assesses the prevalence and severity as well as investigates possible etiological factors of asthma, rhinitis, and eczema.

Statistical analysis

The data from all questionnaires were optically scanned and manually checked for errors. The register data in relation to autoantibody status have been analyzed statistically using two-tailed Fisher exact test after classification of children into islet autoimmunity results of positive or negative at the age of 2.5 yr. All variables were categorized into two categories. We used univariate analysis to identify variables individually predictive of the development of autoantibodies (stage 1). Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using logistic regression with islet autoantibody positivity as the dependent variable and by entering the significant variables (stage 2). Variables were analyzed simultaneously and included in the multivariate model by stepwise forward selection for the significance of the explanatory variable. A p -value below 0.05 or a 95% CI not overlapping the null value 1.00 for the OR was regarded as statistically significant. Intercorrelations between variables were investigated using Spearman's rank correlation coefficients. Statistics were calculated on a PC using the Statistical package for Social Science (SPSS 11.5 software, SPSS Inc, Chicago, IL, USA).

Table 1. The results of univariate analysis of risk factors related to increased levels of β -cell autoantibodies (exceeding the 95th percentile level) in an unselected population of Swedish children from ABIS study

Independent risk factors ≥95%	GADA (N = 342) OR (95% CI)	IA-2A (N = 376) OR (95% CI)	IA-2A and GADA (N = 683) OR (95% CI)
Gender Boys/girls N = 3653/3355		1.3 (1.0–1.6; p = 0.037)	2.2 (1.1–4.6; p = 0.035)
Type of domiciliary: during pregnancy House/apartment N = 4372/2346	1.4 (1.1–1.8; p = 0.009)		
Type of domiciliary: during first year of life House/apartment N = 4069/1534	1.5 (1.1–2.0; p = 0.009)		
Type of domiciliary: during second year of life House/apartment N = 4564/1200	1.4 (1.0–2.0; p = 0.028)		
Type of domiciliary: during pregnancy, first, and second years of life House/apartment N = 5557/1529	1.5 (1.1–2.1; p = 0.005)		
Cat: during first year, at home or at nanny Yes vs. no N = 1398/5810		1.4 (1.1–1.8; p = 0.006)	
Cat: during second year, at home Yes vs. no N = 1417/5791		1.3 (1.0–1.7; p = 0.030)	
Dog: during first year, at home or at nanny Yes vs. no N = 1072/6136	1.3 (1.0–1.8; p = 0.039)		
Dog: during second year, at home Yes vs. no N = 978/6230	1.3 (1.0–1.8; p = 0.048)		
Brother/sister, first year Yes vs. no N = 63/5580	3.3 (1.6–6.7; p = 0.001)		
Maternal smoking, during pregnancy Yes vs. no N = 657/6333		1.6 (1.2–2.2; p = 0.003)	
Domestic smoking; first year >10 vs. ≤10 cigarettes daily N = 102/220		2.9 (1.1–7.7; p = 0.028)	
Maternal smoking, reported second year Yes vs. no N = 683/5233	0.5 (0.3–0.8; p = 0.006)		

ABIS, All Babies in Southeast Sweden; CI, confidence interval; GADA, glutamic acid decarboxylase autoantibodies; IA-2A, autoantibodies to IA-2; OR, odds ratio.

Results

Antenatal and perinatal factors

Male gender of the child implied higher risk for IA-2A (OR 1.3, CI 1.0–1.6; p = 0.037) and for double positivity for GADA and IA-2A (OR 2.2, CI 1.1–4.6; p = 0.035).

Living in a house compared to an apartment during pregnancy implied risk for GADA (OR 1.4, CI 1.1–1.8; p = 0.009).

Mother's smoking during pregnancy implied risk for IA-2A (OR 1.6, CI 1.2–2.2; p = 0.003) (Table 1).

Other variables that were examined but with no significant associations found were infections (including

gastrointestinal infection) during pregnancy, mother's use of antibiotics during pregnancy, perinatal infections, mode of delivery, parent born abroad, and single parenthood.

Environmental factors during first year of life

Living in a house compared to an apartment during first year of life (OR 1.5, CI 1.1–2.0; $p = 0.009$) and getting a brother or sister during first year of life (OR 3.3, CI 1.6–6.7; $p = 0.001$) implied risk for GADA.

Having a cat either at home or at the day-care (nanny) implied risk for IA-2A (OR 1.4, CI 1.1–1.8; $p = 0.006$) and a dog either at home or at the day-care (nanny) implied risk for GADA (OR 1.3, CI 1.0–1.8; $p = 0.039$).

Smoking in the home (more than 10 cigarettes compared to ≤ 10 cigarettes) implied risk for IA-2A (OR 2.9, CI 1.1–7.7; $p = 0.028$) (Table 1).

Other variables that were examined but not significant are infections (including gastrointestinal infection, common cold, infection treated with antibiotics, and influenza) during first year of life, child treated with antibiotics during first year of life, and parents working professionally outside the home.

Environmental factors during the second year of life

Living in a house compared to an apartment during second year of life implied risk for GADA (OR 1.4, CI 1.0–2.0; $p = 0.028$).

Having a cat either at home or at the day-care (nanny) implied risk for IA-2A (OR 1.3, CI 1.0–1.7; $p = 0.030$) and a dog either at home or at the day-care (nanny) implied risk for GADA (OR 1.3, CI 1.0–1.8; $p = 0.048$).

Mother who smoked during the second year of a child's life decreased risk for GADA (OR 0.5, CI 0.3–0.8; $p = 0.006$) (Table 1).

Common cold (in categories; three more times vs. never-twice times) (OR 1.7, CI 1.1–2.7; $p = 0.016$) and gastrointestinal infections (OR 1.5, CI 1.1–2.1; $p = 0.011$) increased risk for IA-2A (Table 2).

Other variables that were examined but not significant are single parenthood, numbers of brothers and sisters, infection (including infection treated with antibiotics, influenza) during second year of life, child treated with antibiotics during second year of life, fathers smoking and domestic smoking, parents' educational level, and parents working professionally outside the home.

History of allergy and asthma

Wheezing more than three times vs. never during the first year of life implied a risk for GADA (OR 1.9, CI

1.0–3.5; $p = 0.042$) and double positivity for GADA and IA-2A (OR 9.1, CI 3.3–25; $p = 0.000$).

Rash on several locations at least 3 months during second year of life implied risk for IA-2A (OR 1.7, CI 1.1–2.6; $p = 0.017$).

Nasal congestion, sneezing, and itchy eyes caused by fur-bearing animals implied risk for IA-2A (OR 2.7, CI 1.3–5.7; $p = 0.008$) during second year of life.

Allergy against egg, cow-milk, fish, and nuts/almonds (one or in combination) implied risk for GADA and IA-2A (OR 4.5, CI 1.9–10.9; $p = 0.001$). Allergy against cow-milk was controlled for lactose intolerance (Table 2).

Logistic regression

When forward stepwise logistic regression model of factors shown in Table 2 was performed wheezing in the child during first year of life increased risk for GADA (OR 2.0, CI 1.1–3.8; $p = 0.031$) and both GADA and IA-2A (OR 10.7, CI 3.9–29.4; $p = 0.000$).

Discussion

Interestingly, we found that the occurrence of wheezing during the first year of life, which has been considered as a risk factor for later development of asthma, was strongly associated with the risk of β -cell autoimmunity at the age of 2.5 yr. The allergic symptoms are based on parental history, and no allergy tests (i.e., skin-prick test or RAST) were performed on these children.

Kero (12) found that asthma tended to be more common in children with T1D than in children without T1D. Also the cumulative incidence of asthma in children with celiac disease and rheumatoid arthritis was significantly higher than in children without those diseases. We could not find support for the inverse association between T1D and the atopic disorders, asthma, eczema, and allergic rhinitis in children reported by some other studies. In a meta-analysis by Cardwell (13) an inverse association between asthma and T1D was revealed (OR 0.82) suggesting that there is a slight but significant reduction in the risk of asthma in children with T1D. Stene (14) used published data on disease occurrence in different countries, showing a strong positive association between the occurrence of T1D and symptoms of asthma at the population level, but not at individual level. The findings suggest that there may be common factors influencing susceptibility to the two disorders at the country level. Factors influencing the proportion of individuals susceptible to inflammatory diseases such as asthma and T1D may cluster in countries, and makes it difficult to compare studies from different populations. There is an increasing incidence of both atopic disease and T1D in the world and it is possible that the relationship between

Table 2. The results of univariate analysis of risk factors (asthmatic/atopic symptoms) related to increased levels of β -cell autoantibodies (exceeding the 95th percentile level) in an unselected population of Swedish children from ABIS study

Independent risk factors: atopy, asthma, and allergy $\geq 95\%$	GADA (N = 342) OR (95% CI)	IA-2A (N = 376) OR (95% CI)	IA-2A and GADA (N = 683) OR (95% CI)
Wheezing; first year (N = 4668) Three-several times vs. never-twice	1.9 (1.0–3.5; $p = 0.042$)		9.1 (3.3–25; $p = 0.000$)
Rash, several locations, 3/12 months: second year (N = 689) Yes vs. no		1.7 (1.1–2.6; $p = 0.017$)	
Allergy vs. fur-bearing animals: second year (N = 132) Yes vs. no		2.7 (1.3–5.7; $p = 0.008$)	
Food allergy (egg, cow-milk, fish, nuts/almonds): second year (N = 285) Yes vs. no			4.5 (1.9–10.9; $p = 0.001$)
Common cold: second year (N = 5859) Three several times vs. never-twice		1.7 (1.1–2.7; $p = 0.016$)	
Gastrointestinal infections: second year (N = 5616) Three-several times vs. never-twice		1.5 (1.1–2.1; $p = 0.011$)	

ABIS, All Babies in Southeast Sweden; CI, confidence interval; GADA, glutamic acid decarboxylase autoantibodies; IA-2A, autoantibodies to IA-2; OR, odds ratio.

asthma and T1D may vary with time in addition to the variation between populations.

We also found that early symptoms of allergic diseases, such as self-reported food allergy and allergic symptoms to fur-bearing animals, were associated with higher frequency of β -cell autoimmunity at the age of 2.5 yr in an unselected cohort of Swedish children. Our study suggests that at least during the first years of life the occurrence of atopic dermatitis and rhinoconjunctivitis is positively associated with the development of T1D related autoimmunity. Our results of the early association of atopic symptoms and β -cell autoimmunity is in agreement with the large epidemiological studies (12, 15) showing that the so-called Th1 and Th2 diseases can co-exist in the same individuals and may even be associated positively.

In a study with children with T1D (16) who underwent skin-prick tests for common aeroallergens, allergic symptoms associated with IgE sensitization were no more probable in children with T1D than in normal control subjects. However, a history of allergic symptoms, especially wheezing (OR 4.3), asthma (OR 5.3), and allergic rhinitis (OR 2.5) was significantly more common in the control group. A study by Stromberg (17) found similar rates of atopic diseases, results of skin-prick tests, and total and specific IgE concentrations in children with T1D and control subjects. No association was found between asthma and T1D, but allergic rhinitis was more prevalent among diabetic children in Sweden.

In favor of the reciprocal regulation of Th1 and Th2 diseases and in contrast to our findings, epidemiological studies have reported that incidence of atopic dermatitis and IgE-mediated allergies are lower among individuals with T1D than in non-diabetic controls. In the EURODIAB ACE substudy 2 (18), data were included from individuals with T1D and reference individuals, and a lower prevalence of atopic diseases was reported among patients with T1D than among non-diabetic individuals (OR 0.70) and most relevant in the age group of 10–14 yr.

Atopic eczema was significantly lower among children with newly diagnosed or who later developed T1D than in the controls (OR 0.49–0.71) (19–22). Hay fever and asthma were not significantly associated with diabetes risk (21). Risk of diabetes was inversely associated with asthma, compared with control population, OR 0.49–0.8 (20, 23). After onset of T1D, diabetic and non-diabetic groups did not differ significantly but a slightly increased risk of atopic eczema after diagnosis of T1D (19).

We studied the early induction of β -cell autoimmunity and its association with atopic symptoms, which is a unique approach and does not directly indicate the association of T1D and atopic disease, but rather the factors related to the triggering of β -cell autoimmunity. Our results suggest that the early triggers of Th1- and Th2-mediated diseases may be the same. These environmental factors may be involved in the poor development of immune regulatory mechanisms, such

as induction of T-regulatory cells, which could impair control of immune responses demonstrated as β -cell autoimmunity and atopic symptoms.

In our study, we found that wheezing during first year of life increased risk for diabetes-related autoantibody-positivity at the age of 2.5 yr, wheezing being the strongest risk factor in the regression analysis. The association of wheezing with β -cell autoimmunity was not explained by infections in our model of regression analysis. Wheezing during the first years of life is associated with respiratory viral infection and it has been suggested to reflect the aberrant immune response to virus. The aberrant immune response being responsible for the wheezing has been suggested to include Th2 profile (24–27). It is not excluded that the association of wheezing with β -cell autoimmunity is explained by infection, not necessarily giving other symptoms than wheezing (28–30). Thus, the otherwise subclinical respiratory infection, which could cause wheezing, was not reported as infections by families in our study. The infants with recurrent wheezing may be prone to asthma later. Douek and co-authors (31) reported the OR for wheezing in children with diagnosed T1D compared to controls being 0.36, and that for wheezing within 12 months was 0.39. The differences between our study and the study by Douek et al. could be explained by differences in the study design; we studied infants and the risk of β -cell autoimmunity, whereas Douk et al. studied children with T1D.

Diabetes-related autoantibodies were related to having a cat at home or at the nanny during the first and second years of life. It has recently been found that wild bank voles develop T1D in association with Ljungan virus, a novel picorna virus (32). It is speculated that bank voles may have a possible zoonotic role as a reservoir and vector for virus that may contribute to the development of T1D in humans. It could be speculated whether that domestic cat captures wild bank voles and thereby transfers the virus to the child.

However, living in a house compared to an apartment during pregnancy and infant years implied risk for GADA. Parents living in a house had significantly higher social status, defined as educational level, parental employment, parents working fulltime vs. part-time, living in a more densely populated areas vs. countryside, parental origin (Swedish native vs. foreign), but these variables were not related *per se* to children's autoantibody status. We also noticed a detrimental effect of early tobacco smoke exposure during pregnancy and during the first year of life, but somewhat surprisingly an inverse association indicating a protective effect of smoking during the second year of life. Exposure to tobacco may temporarily impair the immune system, but the impending effects are complex considering asthma/allergy development.

We conclude that the early induction of β -cell autoimmunity was more often found in children who also had symptoms of atopic diseases suggesting that the factors triggering β -cell autoimmunity and atopic symptoms may be shared. The poor control of immune responses because of the aberrant development of regulatory mechanisms could be an explanation for the predisposition to both atopic diseases and T1D in the same individuals.

Acknowledgements

We are very thankful to all children and their parents who participated in ABIS, as well as to the health centers where all questionnaires were collected and biological samples taken. We are grateful to Gosia Smolinska, Lena Berglert, Cecilia Runnquist, Ingela Johansson, and Mickaela Samuelsson who were of great help in the autoantibody determinations. This study, as a part of the ABIS project, was generously supported by JDRF-Wallenberg foundations (K 98-99D-12813-01A), the Swedish Medical Research Council (MFR; Vetenskapsrådet) K99-72X-11242-05A), the Swedish Child Diabetes Foundation (Barndiabetesfonden), and the Swedish Diabetes Association, Novo Nordisk Foundation.

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