

Coexistence of IgE-Mediated Allergy and Type 1 Diabetes in Childhood

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Key Words

IgE-mediated allergy · Skin-prick test · Type 1 diabetes

Abstract

Background: Autoimmune disorders are considered to be associated with a Th1 immune response while allergic diseases with a Th2 response. We carried out a study to determine whether there is an inverse relationship between allergic diseases in IgE-sensitized children or positive skin-prick test reactions to allergens and type 1 diabetes mellitus (DM1) in children. **Methods:** Sixty-three children with DM1 and 108 controls were enrolled. Parents of all children compiled a questionnaire on allergic diseases. All children underwent skin-prick tests for common aero-allergens and food-allergens. **Results:** A history of allergic symptoms, especially wheezing, asthma and allergic rhinitis was significantly less common in the group with DM1. Allergic symptoms in children with IgE sensitization or parental atopy were no more likely in children with DM1 than in normal control subjects. There was no association between skin-prick test results to inhalants and food allergens and DM1. **Conclusions:** Consistently with the Th1/Th2 paradigm, we observed a reduction in the frequency of allergic symptoms in chil-

dren with DM1. However, our study did not succeed in demonstrating an inverse relation between Th1- and Th2-mediated diseases in children with IgE sensitization or an atopic genetic predisposition.

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Introduction

On the basis of the pattern of cytokine production, functional subsets of the T helper cell clones, called Th1 and Th2, have been reported [1].

Allergic diseases [2], such as asthma, eczema and hay fever, are chronic inflammatory diseases frequently observed in children. Asthma and atopy are thought to be associated with a Th2 cytokine profile which induces an allergen-specific IgE-mediated inflammation [3–5].

On the contrary, autoimmune disorders, such as type 1 insulin-dependent diabetes mellitus (DM1), are characterized by a Th1 phenotype [6]. The Th1 and Th2 response controls the development of the same subset and suppresses the effector cells of the other subset. Therefore, it has been suggested that allergic diseases and DM1 are mutually exclusive and unlikely to be present in the same individual.

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Contrasting data have been reported on the coexistence of DM1 and allergic diseases in questionnaire studies [7–12]. Furthermore, some studies have observed that there is no difference between children with DM1 and controls in the frequency of IgE sensitization [11, 12]. So far, no comparative data are available on the inverse association of allergic symptoms in IgE-sensitized patients [2] with DM1.

To evaluate whether the Th1/Th2 paradigm is supported by in vivo data, we were interested in assessing the frequency not only of allergic diseases but also of positive skin-prick test reactions and atopic allergic diseases in children with DM1 in comparison with a general population. We also investigated whether there was a temporal relationship between DM1 and allergic diseases.

Material and Methods

Study Population

Sixty-three children with DM1 were consecutively enrolled in the patient group at the Regional Center for Childhood Diabetes. There were 34 girls and 29 boys. The mean age was 12.8 years (range 4–19). The age of onset of DM1 was established as the date of the first insulin injection.

One hundred eight nondiabetic children were recruited at school as controls. There were 63 girls and 45 boys. The mean age was 12.2 years (range 3–15 years). Children were examined in the presence of a parent, whose permission to take part in the study was requested.

All children underwent skin-prick tests for common aeroallergens and food allergens. A questionnaire for investigating the frequency of allergic diseases was handed out to parents of all children. All parents completed the questionnaire.

Questionnaire self-reported respiratory allergic symptoms were considered IgE-mediated whether they were associated with a positive skin-prick tests to inhalants [13], self-reported atopic eczema or urticaria whether associated with a positive skin-prick tests to foods.

Questionnaire

Questions about the presence of symptoms often associated with allergy were developed from the International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire [14]. Allergic rhinitis was established through the question: 'Has your child ever had any 'allergy-like' symptoms affecting the nose (e.g., an itchy and/or runny and/or blocked nose, not associated with a cold or the flu)? Hay fever was established by asking whether the child had rhinitis in springtime. Asthma was identified by the question 'Has your child ever had asthma?' It was also asked if the child has ever had wheezing (noisy breathing with a whistling sound coming from the chest) and if a doctor has ever said that the child had asthma. A history of allergic conjunctivitis was established by asking whether the child had any 'allergy-like' symptoms affecting the eyes (e.g. itching, redness, watering). Atopic eczema was identified by the question 'Has your child ever had an itchy rash which was coming and going for at least 6 months?' Furthermore it was asked if the child has ever had eczema defined as itching, chronic or chronically relapsing red patches with

flaking and scaling of the skin. Urticaria was established by asking whether their child has ever had an itching rash, consisting of weals surrounded by variable red circles. It was asked if the child has ever had an allergic reaction caused by the sting of bee or wasp or hornet. Simple questions covered age of onset of allergic symptoms, family history of atopy and identification of the person who completed the questionnaire.

Skin-Prick Test

All children had a skin-prick test using commercial extract for the following aeroallergens (Merck, Milan, Italy) and food allergens (Lofarma, Milan, Italy): grasses, plantain, *Alternaria*, pellitory, birch, hazel, mugwort, *Cladosporium*, *Aspergillus*, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, cat and dog epithelium, milk, egg, cod, tomato, potato, pork, beef, chicken, rabbit, soya, rice, wheat, peanuts, bean, pea. The positive control was histamine 1 mg/ml. The negative control was diluent. The results were evaluated after 10 min. Weals at least 3 mm greater in diameter than weals at the site of the negative control were considered positive. Skin-prick tests were performed if patients were free from antihistamines for 7 days.

Statistics

The frequency of positive skin-prick test results has been reported to be 40% in a general population, that of allergic diseases 20% and that of asthma 10%. Estimating 100 children in the control group, we calculated that we need 26 children for skin-prick tests, 36 for allergic diseases and 42 for asthma in the group with DM1 to provide a 90% power at the 5% level to detect a 50% reduction of each variable in children with DM1.

The χ^2 test, with Yates' correction, was used to compare ordinal variables. Fischer's exact test was used when the expected number of individuals in the cell was less than 5. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. Ages were compared by analysis of variance. Values of $p < 0.05$ were considered significant.

Results

Children with DM1 and controls were comparable concerning both sex and age (table 1). There was no significant difference between the DM1 group and the control group for parental or family (including grandparents, parents, uncles, aunts, brothers and sisters) history of atopy (table 1).

Allergic Symptoms

The prevalence of individual allergic symptoms reported by parents of children with DM1 and controls is displayed in table 2. Thirty-eight percent of the children with DM1 had allergic symptoms compared with 60% of the control children ($p = 0.009$). Among allergic symptoms, only the prevalence of wheezing, asthma and allergic rhinitis was significantly less common in the group with DM1 (table 2).

Table 1. Baseline data

	DM1 group (n = 63)	Control group (n = 108)	OR (95% CI)	p
Age, years				
Mean (SD)	12.857 (4.115)	12.278 (1.685)	–	0.198
Median (SEM)	13 (0.518)	12 (0.162)		
Number (%)				
Boys/girls	29 (46)/34 (54)	45 (41.7)/63 (58.3)	0.837 (0.448–1.566)	0.157
Family history of atopy	47 (74.6)	85 (78.7)	1.258 (0.606–2.613)	0.669
Parental history of atopy	39 (61)	68 (62)	0.956 (0.503–1.815)	1
Questionnaire completed by mother	58 (92)	89 (82.4)	2.476 (0.876–7.000)	0.127
OR = Odds ratio; CI = confidence interval.				

Table 2. Frequency of allergic symptoms in children with DM1 and in controls (number with percentages in parentheses)

Allergic symptoms	DM1 group (n = 63)	Control group (n = 108)	OR (95% CI)	p
Asthma questions				
Wheezing	9 (14.3)	45 (41.7)	4.286 (1.921–9.564)	0.000
Asthma by parents	2 (3.1)	16 (14.8)	5.304 (1.177–23.896)	0.033
Asthma by doctor	2 (3.1)	16 (14.8)	5.304 (1.177–23.896)	0.033
Rhinitis questions				
Allergic symptoms	9 (14.3)	32 (29.6)	2.526 (1.115–5.723)	0.037
Seasonal allergic symptoms	6 (9.5)	22 (20.4)	2.430 (0.928–6.365)	0.102
Conjunctivitis	7 (11.1)	23 (21.3)	2.165 (0.871–5.382)	0.139
Eczema questions				
Itchy rash	9 (14.3)	19 (17.6)	1.281 (0.541–3.034)	0.727
Eczema by parents	8 (12.7)	16 (14.8)	1.196 (0.480–2.977)	0.876
Urticaria	6 (9.5)	11 (10.2)	1.077 (0.378–3.070)	1
Venom allergy	0	2 (1.85)	–	1
Patients positive	24 (38)	65 (60)	2.456 (1.298–4.649)	0.009
OR = Odds ratio; CI = confidence interval.				

Skin-Prick Test

Table 3 shows the proportion of children with positive skin prick tests results. Forty-one percent of the subjects with DM1 and 40% of the control children had at least one positive skin-prick test reaction. Forty-one percent of the children with DM1 (control group: 38%) had positive skin-prick test reactions to inhalants, 4% of the children with DM1 (control group: 2%) to food allergens (table 3). No significant association was found between DM1 and skin-prick test results to grasses, *Alternaria* and house dust mites. Since positive skin-prick test reactions to plantain, pellitory, birch, hazel, mugwort, *Cladosporium*, *As-*

pergillus, cat and dog epithelium and single foods were observed only occasionally, data were not shown.

Atopy and Allergic Symptoms

Wheezing, asthma, rhinitis, conjunctivitis were defined as atopic if they were associated with positive skin-prick test reactions to aeroallergens in the same individual. Eczema and urticaria were considered atopic in children presenting positive skin-prick test reactions to food allergens. Table 4 provides details on the prevalence of atopic allergic symptoms. Thirteen (20%) of the children with DM1 had atopic allergic symptoms (control group:

Table 3. Skin-prick test results in the study groups (number with percentages in parentheses)

Positive skin-prick test reaction	DM1 group (n = 63)	Control group (n = 108)	OR (95% CI)	p
Patients positive to any inhalant allergen	26 (41.3)	42 (38.9)	0.906 (0.481-1.706)	0.885
Grasses	12 (19)	24 (22.2)	1.214 (0.559-2.637)	0.767
<i>Alternaria</i>	2 (3.2)	9 (8.3)	2.773 (0.580-13.262)	0.332
House dust mites	17 (27)	24 (22.2)	0.773 (0.377-1.585)	0.605
Patients positive to any food allergen	3 (4.7)	3 (2.7)	0.571 (0.112-2.921)	0.671
Patients positive to at least 1 allergen	26 (41.3)	44 (40.7)	0.978 (0.520-1.840)	1

OR = Odds ratio; CI = confidence interval.

Table 4. Frequency of allergic symptoms in children with positive skin-prick test in DM1 and control groups (number with percentages in parentheses)

Atopic allergic symptoms	DM1 group (n= 63)	Control group (n = 108)	OR (95% CI)	p
Asthma questions				
Wheezing	4 (6.3)	18 (16.6)	2.950 (0.951–2.950)	0.088
Asthma by parents	1 (1.58)	7 (6.5)	4.297 (0.516–35.764)	0.260
Asthma by doctor	1 (1.58)	7 (6.5)	4.297 (0.516–35.764)	0.260
Rhinitis questions				
Allergic symptoms	7 (11.1)	22 (20.4)	2.047 (0.020–5.108)	0.179
Seasonal allergic symptoms	5 (7.9)	15 (20.4)	1.871 (0.646–5.422)	0.357
Conjunctivitis	5 (7.9)	14 (12.9)	1.728 (0.591–5.048)	0.449
Eczema questions				
Itchy rash	1 (1.5)	1 (0.9)	1.726 (0.106–28.081)	1
Eczema by parents	0	1 (0.9)	–	1
Urticaria	1 (1.5)	0	–	0.784
Patients positive	13 (20.6)	35 (32.4)	1.844 (0.888–3.831)	0.140

OR = Odds ratio; CI = confidence interval.

32%; $p = 0.140$). Children with DM1 were not less likely to have the remaining atopic allergic symptoms than controls (table 4). Wheezing in nonatopic children was significantly less common in the DM1 group [OR (95% CI) = 3.867 (1.405–10.638); $p = 0.011$]. We could find no difference in the frequency of the asthma, rhinitis, conjunctivitis, eczema or urticaria in nonatopic children between DM1 and control groups.

There were 18 (28%) children with parental atopy and allergic symptoms in the DM1 group and 38 (35%) in the control group [OR (95% CI) = 1.357(0.691–2.664); $p = 0.471$]. Both in the DM1 and control groups, there was no association between parental atopy and the presence of allergic symptoms in the child.

Age of Onset of Allergic Symptoms

The mean age of onset of DMI was 8.07 years $\pm$ SD 3.93 (median: 7.9; SEM: 0.49).

We could find no significant difference between the two groups in the age of onset of allergic symptoms (DM1 group: mean 4.94 years $\pm$ SD 4.34 (median: 3.5; SEM: 1.02); control group mean 5.9 years $\pm$ SD 3.93 (median: 6; SEM: 0.55; $p = 0.391$). Fourteen out of 18 children of the DM1 group had a history of occurrence of allergic symptoms before the onset of DM1. In these 14 diabetic children, the mean age of onset of allergic symptoms was $3.42 \pm$ SD 3.45, similar to that of the controls ($5.90 \pm$ SD 3.93; $p = 0.083$).

The mean age of onset of atopic allergic symptoms was 5.33 ± 4.58 years (median: 4; SEM: 1.52) in the DM1 group and 6.96 ± 3.63 (median: 7; SEM: 0.67) in the control group ($p = 0.276$). There was no significant difference between DM1 and control groups in the mean age of onset of atopic asthma ($p = 0.128$) or atopic allergic rhinitis ($p = 0.353$).

Before the onset of DM1, atopic allergic symptoms occurred in 10 (76%) out of 13 diabetic children. There was no difference between the mean age of onset of allergic symptoms in 10 diabetic children, who had allergic symptoms before the onset of DM1, in comparison with controls (4.28 ± 4.42 vs. 7 ± 3.63 ; $p = 0.098$).

Discussion

The results of the present survey show that children with DM1 have reduced frequency of questionnaire self-reported allergic symptoms. However, our findings provide evidence that there is no inverse relationship between allergic symptoms in IgE-sensitized children and DM1. Furthermore, our study failed to demonstrate a negative association between IgE sensitization to inhalants and food allergens and DM1.

A number of questionnaire surveys [7–11, 15] have found conflicting results on the prevalence of allergic disorders in children with DM1. In a population-based case-control study in children, Douek et al. [10] found that wheezing was inversely associated with DM1, reporting a prevalence of 27% in children with DM1 and 51% in the controls. Along this line, other studies have found that children with a history of any one allergic disease, particularly asthma [7], or of atopic dermatitis [8, 9], had a significantly decreased risk of developing DM1. Mattila et al. [15] sent a questionnaire to 819 patients with DM1 and controls aged 10–27 years. They received responses from 347 (42%) patients and 483 (59%) controls and reported that the risk of DM1 was inversely associated with a history of asthma or of allergy to animal dust. These observations are in agreement with the results of our study. We found that self-reported allergic symptoms, particularly wheezing, asthma and allergic rhinitis were less common in children with DM1 compared with normal controls. In contrast to previous reports, Sheikh et al. [11] who reviewed data of a sample of 20,009 adult subjects from the Third National Health and Nutrition Survey conducted from 1988 to 1994, found that reported physician-diagnosed asthma and hay-fever were not inversely associated with DM1 in adults. Differences in questionnaire

items, selection of patients, age of study subjects and age of onset of diseases may explain the inconsistent findings of previous studies.

Self-reported allergic symptoms can reflect reactions that are not correlated with IgE sensitization. Earlier surveys [13, 14] found that 50–80% of patients reporting allergic diseases were sensitized to allergens. This is consistent with our findings. Furthermore, a Th2 cytokine profile is associated with atopic asthma but not with non-atopic asthma [17]. Therefore, we combined the questionnaire with skin-prick test results. Our findings showed that allergic diseases in atopic children were not inversely associated with DM1. On the other hand, nonatopic diabetic children were significantly less likely to have wheezing. Moreover, our findings confirm that IgE sensitization, defined by positive skin-prick test results, in children with DM1 is similar to that of the general population [11, 12].

Several characteristics and limitations of the present survey should be kept in mind to correctly interpret the study findings. First, no sample is large enough to exclude differences between groups, because we can never be sure that the sample and the population are as we expect. However, we did not select study subjects, and data were obtained with standardized methods in both patient and control groups. Therefore, we think that our findings are reliable, and our sample is sufficiently large to demonstrate that atopy and DM1 may exist in the same individual. Secondly, allergic diseases were ascertained on the basis of parental questionnaire reports. This raises the possibility of recall bias. However, all questionnaires were completed with a research assistant present to reply to any question. Parents were told that there were no right or wrong answers. Frequency of respiratory symptoms and eczema was investigated using items of the standardized ISAAC questionnaire which have been tested and validated [14]. Furthermore, we obtained information by the same procedures in both DM1 and control groups. Therefore, we believe that data bias is unlikely. Finally, the clinical relevance of a positive skin-prick test should be confirmed by a positive challenge test to allergen, which was not done in our study and may be considered as another possible weakness. However, there is a good correspondence between positive challenge and positive skin-prick test to inhalants in patients with a history of allergic diseases [18–20]. So, in clinical practice a large-scale provocation test to aeroallergens is not needed.

Genetic and environmental factors might be responsible for the incomplete inverse association between allergic symptoms and DM1. According to the 'hygiene hypothe-

sis', the increase in allergic diseases, skin prick test positivity and allergen-specific IgE in smaller and more affluent families is explained by a decreased frequency of infections in childhood, which reflects a reduced exposure to transmittable diseases [21]. Studies conducted at the population level, showed a strong positive association between DM1 and allergic diseases and an increase in the incidence of both [23, 24]. These findings may suggest that common environmental factors, such as reduced exposure to infections in the first years of life, may alter immune system maturation determining individual susceptibility to both allergic diseases [24] and DM1 [25]. This is not in contrast with the 'hygiene hypothesis', since it cannot be ruled out that common environmental factors might provoke the occurrence of one disease and confer partial protection against another [26]. Although this might explain the decreased frequency of allergic diseases and nonatopic wheezing in our DM1 group, it is unlikely to account for the lack of association between atopic allergic disorders and DM1. We believe that it is the consequence of a strong genetic predisposition that prevails over environmental factors. This is consistent with findings that family size protects against atopy only in subjects without parental history of allergy [27]. In this context, it may be worth noting that we found no decrease in allergic diseases in diabetic children with parental atopy in comparison with controls with parental atopy.

The possible mechanisms underlying the decrease in allergic symptoms among children with DM1 are unclear. It has been suggested that this decrease could result from negative interactions between Th1 and Th2 subsets. Specific allergen stimulation elicits an increase in Th2 cells [28] which control and amplify the allergic inflammatory response. It has been shown that autoimmune disorders are Th1-mediated. Th1 cell activation by microbial substances has a protective effect against sensitization and onset of allergic diseases by downmodulating the effects of Th2 cells [29]. However, there is some support for the view that the experimental Th1/Th2 paradigm may be an oversimplification of the complex immune system interactions in asthma. Infections can provoke not only Th1 responses but also asthma exacerbations. A possible explanation is that a Th1 immune response in asthmatic patients [30] would be responsible to some degree for both the development of bronchial hyperreactivity and the triggering of asthma symptoms upon microbial exposure [31]. Furthermore, different types of regulatory T cells such as Th3 cells, Tr cells, CD25+ T cells and NKT cells have been suspected to be involved in controlling the development of allergic diseases [32]. On the other hand,

both Th1 and Th2 cytokines play a direct role in β islet cell destruction, suggesting that DM1 is a Th1- and Th2-mediated disease [33]. It has also been observed that NOD mice prone to autoimmune diabetes develop a Th2-mediated disease, namely experimental allergic asthma [34]. In agreement with these findings, we showed that positive skin-prick test results or atopic allergic symptoms are not inversely associated with DM1. Taken together, these data reflect the coexistence of Th1 (DM1) and Th2 (atopy) diseases in the same individual.

It is interesting to speculate on the hypothesis that in children with DM1 the Th1 response may end when the islets are destroyed, permitting the subsequent onset of allergic diseases by a Th2 immune mechanism. A history of allergic diseases, particularly asthma [7] or atopic dermatitis [8, 9], protects against the onset of DM1 in childhood. At variance, we found that in most diabetic children, both allergic diseases and IgE sensitization developed before the occurrence of DM1. Longitudinal studies are needed to clarify whether the Th1/Th2 paradigm should be considered a dynamic immunologic process in the natural course of the disease.

Lastly, another possibility is that a variation in the level of substances released into the circulation might be diminishing the frequency of allergic diseases in children with DM1. In this respect, it might be relevant that in an animal model, insulin deficiency reduces the inflammatory component of asthmatic responses [35].

Using a case-control design, we have found that atopy and autoimmune diseases which are considered respectively Th2- and Th1-mediated are not mutually exclusive. Therefore, further studies are warranted to understand why allergic symptoms among children with DM1 have decreased. Such studies will need to take into account confounding variables, such as the sequence of occurrence of allergic symptoms; environmental factors, including different types of early childhood infections; markers of immune response or genetic differences, in atopic and nonatopic patients with DM1.

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