Atopy in Children and Adolescents with Insulin-Dependent Diabetes Mellitus

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Abstract

Background: Insulin-dependent diabetes mellitus is dominated by a Th1 response whereas atopic diseases such as asthma, eczema and allergic rhinitis are characterized by a Th2 response. Because it is known that Th1 and Th2 cells reciprocally counteract each other, it can be speculated that the prevalence of Th2-mediated diseases is lower in patients with a Th1-mediated disease.

Objectives: To compare the prevalence of atopic diseases among children with IDDM and age-matched controls.

Methods: The study group comprised 65 children with IDDM attending the pediatric endocrinology clinic at the Wolfson Medical Center. The control group consisted of 74 non-diabetic children who presented at the emergency room due to an acute illness (burns, abdominal pain, fever, head trauma). Patients were asked to complete a detailed questionnaire on their history of personal and familial atopic and autoimmune diseases. In addition, a total serum immunoglobulin E concentration and the presence of IgE antibodies to a panel of relevant inhalant allergens were analyzed.

Results: Children with IDDM and their first-degree relatives had a significantly higher prevalence of other autoimmune diseases such as thyroiditis and celiac as compared to controls. The two groups had a similar prevalence of atopic diseases with respect to history, total serum IgE, or the presence of IgE antibodies to a panel of relevant inhalant allergens.

Conclusions: The prevalence of atopic diseases in IDDM patients was similar to that in the normal population. Our results suggest that the traditional Th1/Th2 theory to explain the complexity of the immune response is oversimplified.

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T helper cells play an important role in the pathophysiology of atopic and autoimmune diseases. These cells are classified into two subsets according to the cytokines they secrete. Th1 cells produce mainly interferon-gamma, interleukin-2, IL-12 and tumor necrosis factor-alpha and are involved in intracellular infections and autoimmune diseases. In contrast, Th2 cells produce IL-4, IL-5, IL-13, and IL-10 and are associated with extracellular infections and atopic diseases. It is believed that the same T cell precursor (designated Th0), a mature naïve CD4+ T lymphocyte, is capable of developing either a Th1 or Th2 phenotype. Once a T cell immune response begins to develop along one pathway, it tends to progressively polarize in that direction. Th1 and Th2 cells reciprocally inhibit each other by production of their specific cytokines [1,2].

Autoimmune diseases such as insulin-dependent diabetes mellitus, rheumatoid arthritis and autoimmune thyroiditis are mainly considered as Th1-mediated organ-specific autoimmune diseases. In contrast, in atopic diseases such as asthma, eczema and hay fever, exposure to aero-allergens promotes the differentiation of Th cells towards Th2 cells which causes B lymphocytes to produce specific IgE against allergens. Given the polarization of the developing T cells into two different subsets of cells, it is reasonable to speculate, although this description is simplistic, that autoimmune and allergic diseases represent two ends of the spectrum of immune responses and that these two types of disorders would be mutually exclusive.

Studies have revealed conflicting results regarding the association of atopy/allergic disease and autoimmune disorders. Of note is that most of these reports were based on patients' reports of physician-diagnosed diseases and not on objective parameters such as skin-prick testing or specific IgE in blood samples. Thus, the aim of our study was to assess the prevalence of clinical and laboratory manifestations of atopic diseases in children and adolescents with IDM

Patients and Methods

The study group consisted of 65 children and adolescents with IDDM attending the Outpatient Endocrinology Clinic at the Wolfson Medical Center. Their ages ranged from 15 months to 24 years. Diagnosis of IDDM was based on typical clinical and laboratory findings together with the presence of antibodies against certain pancreatic particles and low levels of native insulin (C peptide). The degree of metabolic control in patients with IDDM was defined according to glycated hemoglobin A1 level. The control group consisted of non-diabetic children and adolescents who presented at the pediatric emergency room at the same hospital due to acute illness (such as burns, abdominal pain, fever, head trauma, etc.).

The subjects or their parents were asked to complete a detailed questionnaire regarding their family and personal history of atopic diseases such as eczema, allergic rhinitis, asthma, food

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IDDM = insulin-dependent diabetes mellitus
Ig = immunoglobulin
Th = T helper
IL = interleukin

and drug allergy, and of autoimmune diseases such as diabetes mellitus, thyroid disease, celiac disease, rheumatoid arthritis, hematological disorders, psoriasis and inflammatory bowel diseases. Asthma was defined as recurrent wheezing episodes. Blood was drawn from all patients as part of their routine evaluation in the endocrinology unit or the emergency room. Serum samples were frozen at -20ºC until assayed. The study was approved by the medical ethics committee of the Wolfson Medical Center and the Ministry of Health.

Laboratory workup

Total serum IgE concentration was analyzed with VIDAS Total IgE based on the enzyme-linked fluorescent assay technique, as recommended by the manufacturer (Biomerieux, F-69280 Marcy l'Etoile, France, bioMérieux Website: www. biomerieux.com). A positive value was determined as a value of two standard deviations above the mean age-matched control population levels. Levels of specific IgE antibodies to relevant inhalant allergens (house dust mite, dog, cat, grass, weeds, molds, olive, cypress) were assessed by IMMULITE 2000-Advanced Immunoassay System of DPC (Diagnostic Products Corporation). A positive value was determined as a value of 0.35 ku/L or higher.

Statistical methods

Analysis of data was carried out using SPSS statistical analysis software (SPSS Inc., Chicago, IL, USA, 1999). For continuous variables, such as age and years since diagnosis of diabetes, descriptive statistics were calculated and reported as mean ± standard deviation. Normalcy of distribution of continuous variables were assessed using the Kolmogorov-Smirnov test. All continuous variables were normally distributed and were compared by treatment assignment using the *t*-test for independent samples. Categorical variables such as gender and the presence of specific medical conditions were described using frequency distributions. The chi-square test with 99% Monte Carlo confidence intervals was used to detect differences in categorical variables by treatment groups. Logistic regression analysis was used to model specific outcomes including age as a covariate and to develop odds ratios with 95% confidence intervals. All tests were two-sided and considered significant at $P < 0.05$.

Results

Altogether, 65 IDDM patients and 74 non-diabetic age-matched controls were recruited for this study. There was no significant difference between the two groups in terms of age, gender or ethnicity. Table 1 summarizes clinical and laboratory characteristics of IDDM patients. Diagnosis of IDDM was made at a mean age of 9.1 years (range 7 months to 17 years) and the duration of diabetes was 5.54 ± 4.06 years.

Sixteen IDDM patients (24.6%) reported additional autoimmune diseases, as compared to only two (2.7%) of the control patients ($P < 0.001$). Thyroiditis was the most prevalent autoimmune disease to be reported (n=10), followed by celiac disease (n=3), psoriasis (n=1), idiopathic thrombocytopenic purpura (n=1) and vitiligo (n=1). To control for the effect of age, a logistic regression analysis of other autoimmune diseases was undertaken. Both diabetes mellitus and age were positively associated with autoimmune disease: age odds ratio 1.13, 95% confidence interval 1.02–1.25, $P = 0.016$; diabetes mellitus OR = 10.9, 95% CI 2.37–50.4, $P = 0.002$. This means that for each additional year of age, the probability of reporting another autoimmune disease increased by 13%. Autoimmunity in the family of diabetic patients was reported in 28.6% as compared to 9.6% of control patients ($P = 0.002$).

Onset of atopy, i.e., symptoms such as wheezing, atopic dermatitis, food or drug allergy, during infancy was reported by 50–60% in both groups. Among diabetics, onset of atopy preceded the onset of IDDM in 77.4%. Family history of any atopy was similar in both groups (49.2% among IDDM patients versus 47.9% among control patients).

The prevalence of various atopic symptoms is summarized in Table 2. No significant difference was found in the prevalence of atopic dermatitis, allergic rhinitis, conjunctivitis, hay fever, food allergy and asthma between the two groups. Although the prevalence of drug allergy, visit to an allergist, skin-prick test or RAST (radioallergosorbent) test was lower among IDDM patients

Table 1. Characteristics of 65 IDDM patients

Onset of IDDM (yrs)	9.1 ± 4.11
Years since diagnosis	5.54 ± 4.06
Units of insulin/kg/day	0.87 ± 0.33
HbA1C levels (mg/dl)*	9 ± 2.91
Positive anti-pancreas antibodies at diagnosis n (%)	46 (70.7)
Low levels of C-peptide at diagnosis n (%)	50 (77)

* Reference values for healthy control subjects are 5–8 mg/dl.

Table 2. Allergic symptoms among IDDM and control patients

	IDDM n (%)	Control n (%)	*P*
Onset of atopy			
Infancy	18 (66.7)	17 (54.8)	NS
Childhood	9 (33.3)	12 (38.7)	NS
Adolescence	0 (0)	2 (6.5)	NS
Atopic dermatitis	5 (7.7)	9 (12.2)	NS
Persistent allergic rhinitis	2 (3.1)	4 (5.4)	NS
Allergic conjunctivitis	2 (3.1)	3 (4.1)	NS
Seasonal allergic rhinitis	4 (6.2)	6 (8.1)	NS
Asthma	15 (23.1)	22 (29.7)	NS
Food allergy	5 (7.7)	8 (11.1)	NS
Drug allergy	2 (3.1)	5 (6.8)	NS
Visit to allergist	4 (6.2)	9 (12.3)	NS
Prick or RAST test	3 (4.7)	7 (9.5)	NS
Any type of atopy	26 (40)	30 (40.5)	NS

OR = odds ratio
CI = confidence interval

Table 3. High IgE levels among IDDM and control patients

	IDDM n (%)	Control n (%)	*P*
Total IgE	19 (32.8)	17(23.9)	NS
Specific IgE to			
Mite	15 (23.8)	14 (19.2)	NS
Cat	3 (4.8)	2 (2.7)	NS
Dog	0 (0)	0 (0)	NS
Mold	1 (1.6)	0 (0)	NS
Grass	11 (17.5)	8 (11)	NS
Weeds	0 (0)	0 (0)	NS
Olive	7 (11.1)	4 (5.5)	NS
Cypress	1 (3.1)	0 (0)	NS
Pecan	1 (1.6)	1 (1.4)	NS
Any specific IgE	21 (33.3)	19 (26)	NS

as compared to control patients, this difference was not statistically significant.

Table 3 summarizes the blood results for the presence of high total IgE and specific IgE to various inhaled allergens. Among diabetics 32.8% had high levels of total IgE for age as compared to 23.9% of non-diabetics. Positive test for any specific IgE was detected in 33.3% of control subjects, as compared to 26% of the diabetics. These findings were not significantly different.

Discussion

In our study the prevalence of atopy – such as clinical manifestations of atopic disease, total IgE and sensitivity to aeroallergens – in diabetic patients was similar to that in healthy controls. In addition, children with IDDM and their first-degree relatives had a significantly higher prevalence of other autoimmune diseases such as thyroiditis and celiac disease, as previously reported by us [3].

Our findings are in contrast to several previous studies that found an inverse relationship between atopic parameters (such as bronchial reactivity, asthma and atopic dermatitis) and IDDM [4-8]. The EURODIAB [9] – a multicenter, population-based case-control study – found a decreased prevalence of atopic diseases, in particular asthma, in children with IDDM, but only in West European centers. The risk reductions associated with the atopic diseases were marked in children in the 10–14 year age group. A recent survey of almost 500,000 Israeli adults at the time of their enrollment into military service between 1980 and 2003 found that asthma prevalence was inversely correlated with a number of autoimmune diseases that were also diagnosed at enrollment [10]. Cardwell et al. [11] performed a meta-analysis summarizing the association between IDDM and atopic diseases (asthma, eczema, allergic rhinitis) in children. The analysis suggests that there is a small but significant reduction in the prevalence of asthma in children with IDDM, but the findings for the other atopic diseases are less conclusive. However, most of the studies were epidemiological and relied on patients' and/or physicians' reports rather than objective laboratory investigations such as IgE levels and sensitivity to aeroallergens.

In addition to these epidemiological studies there is laboratory evidence that supports the Th1/Th2 paradigm. Rapaport and co-workers [12] reported that stimulated peripheral blood mononuclear cells of IDDM patients had early decreased secretion of Th2 cytokines and a late secretion of Th1 cytokines as compared to normal controls [12].

In contrast to the "traditional" concept of an inverse association between atopy and autoimmunity, some investigators have shown that autoimmune Th1 diseases such as thyroiditis, IDDM, celiac, psoriasis and rheumatoid arthritis in both adults and children could coexist with Th2-mediated diseases [13-16], suggesting that the Th1/Th2 paradigm is oversimplified. Furthermore, the increasing prevalence of atopic diseases worldwide is accompanied by a parallel rise in autoimmune Th1-mediated diseases such as IDDM [17]

Consistent with our findings, Stromberg et al. [13] reported no differences in the prevalence of atopic diseases in children with IDDM and normal controls, as defined by history, clinical features, skin-prick tests, serum total IgE and specific IgE antibodies to allergens. Duran and colleagues [14] found that atopy frequencies were similar in an adult population of type 1 diabetic patients and controls based on questionnaire, skin-prick test, pulmonary function test and methacholine challenge test. These studies together with our study are based on objective parameters rather than subjective evidence alone.

Laboratory support for our findings came from two elegant studies published recently. Maier et al. [18] investigated whether the Th2-related phenotype (total circulating IgE) and a Th1-mediated disease (IDDM) share genetic loci. They found that allelic variation in the IL-13 gene is associated with IgE levels variance and atopic illness but has no detectable effect in type 1 diabetes [18]. Heaton et al. [19] reported that Th1 cytokine secretion and not Th2 was associated with the size of immediate hypersensitivity skin test to allergens and bronchial hyper-responsiveness in a large cohort of IDDM children, suggesting that Th1 cytokine secretion may either be pro- or anti-inflammatory in the same autoimmune disease [20,21].

It should be mentioned that the small size of our groups prevents us from any definite conclusions, and that a larger sample size might have demonstrated a significant difference in some atopic categories. It is also possible that atopic manifestations in children with chronic disease such as IDDM are more readily diagnosed because of frequent medical visits. However, such a bias is unlikely in our study since our findings include also objective laboratory parameters in both groups.

The "classical" Th1/Th2 paradigm is currently undergoing increased scrutiny and includes, besides cytokines, other shared environmental and genetic risk factors that determine the balance between Th1 and Th2 subsets and underlie the pathogenesis of atopy and autoimmune disorders. The parallel appearance of asthma and autoimmune conditions in the same patients may reveal aberrations of the immune system regulation instead of polarization towards Th1 or Th2 domination as a common pathophysiological mechanism. The new paradigm identifies additional lymphocyte subsets, such as Th17 T cells, which dif-

ferentiate along a pathway that is totally independent of Th1 and Th2 cells, regulatory T cells (Treg), Th2-like natural killer T cells and novel soluble transcription factors [22-24]. Indeed the role of these cells in the pathogenesis of autoimmune as well as atopic diseases has recently been extensively studied 25].

In summary, we did not find a significant difference in the prevalence of atopy among IDDM patients as compared to the general population based on clinical and laboratory parameters. Our findings suggest that the traditional Th1/Th2 theory is oversimplified in explaining the complexity of the immune response in autoimmune and atopic diseases.

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