

Prevalence of atopy in children with type 1 diabetes mellitus in central Taiwan

Shiou-Tzong Tzeng, San-Ging Hsu, Lin-Shien Fu, Chin-Shiang Chi

Division of Immunology and Nephrology, and Division of Endocrine and Metabolism, Department of Pediatrics, Taichung Veterans General Hospital, Taichung, Taiwan

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Background and Purpose: Atopic diseases, including asthma, eczema and allergic rhinitis, are characterized by a chronic inflammatory reaction mediated by T helper 2 (Th2) cells, while type 1 diabetes mellitus (T1D) is mediated by T helper 1 (Th1) cells. The 'balance' between Th1 and Th2 cells appears to be vitally important. Hence, it is a plausible hypothesis that the prevalence in Th2-mediated disease would be lower in patients with Th1-mediated disease. The aim of this study was to compare the prevalence of atopic diseases between children with T1D and age-matched controls, and investigate possible factors that influence the prevalence of atopic disease.

Methods: Parents of children with T1D in Taichung Veterans General Hospital were requested by pediatricians to complete the International Study of Asthma and Allergies in Childhood questionnaire on the prevalence of atopic diseases. Responses were compared with an age-matched control group.

Results: Questionnaires were evaluated from 100 T1D patients and 194 controls. After age-matching, the questionnaires of 54 T1D patients were included. Symptoms of asthma, allergic rhinitis and eczema were reported less often in the group of children with T1D compared with the control group (wheeze with exercise, $p=0.044$; nasal symptoms with itching eyes in the past 12 months, $p=0.048$; nasal allergy ever, $p=0.038$; skin rash in the past 12 months, $p=0.044$). In addition, the proportion of T1D patients with any asthmatic symptom (such as wheezing once in life, wheezing in the past 12 months, wheezing with exercise and dry cough at night in the past 12 months) was significantly lower than in controls (20.4% vs 36.6%, $p=0.036$).

Conclusions: These results indicate that patients with T1D have a lower prevalence of atopic symptoms, especially asthma, which is consistent with the Th1/Th2 polarization concept. Environmental factors are another direct influence on the development of atopy in T1D patients.

Key words: Asthma; Diabetes mellitus, type 1; Hypersensitivity; Risk factors; Th1 cells; Th2 cells

Introduction

Type 1 diabetes mellitus (T1D), previously known as insulin-dependent diabetes mellitus, develops after a period of autoimmunity against the insulin-producing beta (β)-cells in the pancreas. It is generally accepted that both genetic [1] and environmental factors, such as early virus infection [2], play important roles in causation and the loss of β -cells, that is eventually due to an autoimmune process. Several aspects about the immune system are still obscure, but increasing evidence

suggests that T helper cells, especially T helper 1 (Th1) cells, play a key role in the pathogenesis of T1D [3].

Th1 and T helper 2 (Th2) cells can be distinguished by their patterns of cytokine production. Th1 cells produce interferon-gamma, interleukin (IL)-2, and tumor necrosis factor- β , which are mainly involved in intracellular infection and autoimmune diseases. Th2 cell-derived cytokines are IL-4, IL-10 and IL-13, which are associated with extracellular infections and atopic diseases. Th1 and Th2 cells mutually repulse each other by production of specific cytokines [4].

The Th1 phenotype was considered to be associated with autoimmune diseases, including rheumatoid arthritis, juvenile rheumatoid arthritis, T1D, and multiple sclerosis [5,6]. On the other hand, atopic diseases appear

*Corresponding author: Lin-Shien Fu, Department of Pediatrics, Taichung Veterans General Hospital, No.160, Sec.3, Chung-Kang Rd., Taichung 407, Taiwan.
E-mail: linshienfu@yahoo.com.tw*

to be mediated by Th2 activity [7]. Some animal model studies have demonstrated β -cell protection by skewing the pattern of cytokines, which shifts T cells from a Th1 to a Th2 profile [3].

Against the background of the characteristic mutual inhibition of the Th1/Th2 system, we hypothesized a lower predisposition to atopy in patients with T1D, and investigated the prevalence and severity of asthma, allergic rhinitis and eczema symptoms in Taiwan elementary school-children with T1D and an age-matched control group.

Methods

Study group

100 patients with T1D, attending the Department of Pediatrics, Taichung General Veteran Hospital were assessed by use of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, Chinese edition [8] completed by their parents. Fifty four patients aged 7 to 14 years who fulfilled the criteria of T1D were included in this study.

Control group

In order to minimize the likelihood of differences between the study groups, we selected control children whose area distribution was similar to the children with T1D. 16,322 elementary school students, 7-14 years of age, living in Taichung city in Taiwan were included. ISAAC questionnaires were completed by their parents. 200 questionnaires were collected in random sampling of this group. Finally, 194 schoolmates of the study subjects were invited to participate as control subjects. They were non-diabetic and matched for age and gender.

Statistical methods

Clinical characteristics in the two groups were compared by means of Mann-Whitney *U* test or Yate's correction of contingency, as appropriate. Symptoms of asthma,

rhinitis and eczema were compared by Yate's correction of contingency or Fisher's exact test, according to statistically expected value. A *p* value of <0.05 was considered significant. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS; Version 10.1.3c, Chinese edition; SPSS, Chicago, IL, USA).

Results

In the T1D group, we received 100 completed questionnaires. The age range of participants was 3 to 25 years old. In the control group, 6 questionnaires were not completed and 194 questionnaires were adopted for the study. All children with T1D younger than seven years old and older than 14 years old were excluded from the statistical comparisons, as the control group consisted of children aged between 7 and 14 years only. The basic data were not significantly different between the T1D and control groups (Table 1).

Symptoms of asthma and allergic rhinitis were reported less frequently in children with T1D than in the control group. In the core questionnaire for rhinitis, patients with T1D showed a significant decrease in positive responses to the question "In the past 12 months, has this nose problem been accompanied by itchy-watery eyes" ($p=0.048$) and also the question "Have you ever had hayfever or allergic rhinitis" ($p=0.038$) [Table 2]. In addition, we also compared the percentage of positive asthma, rhinitis and eczema symptoms between these two groups. As shown in Table 3, the prevalence of asthma in children with T1D was apparently lower compared with the control group ($p=0.036$). However, there was no statistically significant difference in prevalence of atopic symptoms between T1D patients and controls.

We also investigated the possible influence of certain factors (including breast-feeding, home pets and family

Table 1. Comparison of clinical characteristics in children with type 1 diabetes mellitus (T1D) and controls

Characteristic	T1D (n = 54)	Controls (n = 194)	<i>p</i>
Age (years)	10.74 ± 2.40 ^a	10.32 ± 1.94 ^a	0.171 ^b
Birth weight (kg)	3.21 ± 0.51 ^a	3.37 ± 2.46 ^a	0.837 ^b
Gender (male; no. [%])	25 (46.3)	105 (54.1)	0.387 ^c
Breast-feeding (no. [%])	15 (27.8)	69 (35.6)	0.364 ^c
Passive smoking (no. [%])	28 (51.9)	100 (51.5)	1.000 ^c
Pets (no. [%])	12 (22.2)	34 (17.6)	0.568 ^c

^aMean ± standard deviation.

^bMann-Whitney *U* test.

^cYate's correction of contingency.

Table 2. Prevalence of atopy symptoms in children with type 1 diabetes mellitus (T1D) and controls

Questions	T1D (n = 54) No. (%)	Controls (n = 194) No. (%)	Odds ratio (95% CI)	<i>p</i>
Asthma questions				
Wheezing ever in life	5 (9.3)	31 (16)	0.537 (0.198-1.454)	0.307 ^a
Wheeze in the past 12 months	4 (7.4)	15 (7.7)	0.995 (0.303-3.005)	1.000 ^b
Wheeze with exercise	1 (1.9)	24 (12.4)	0.134 (0.018-1.012)	0.044 ^a
Dry cough at night in the past 12 months	6 (11.1)	48 (24.8)	0.38 (0.153-0.944)	0.050 ^a
Rhinitis questions				
Nose symptoms ever	23 (42.6)	88 (45.4)	0.894 (0.486-1.643)	0.836 ^a
Nose symptoms in the past 12 months	18 (33.3)	84 (43.3)	0.655 (0.348-1.233)	0.246 ^a
Nose symptoms with itchy-watery eye in the past 12 months	8 (14.8)	57 (29.4)	0.418 (0.186-0.941)	0.048 ^a
Hay fever or nasal allergy ever	12 (22.2)	75 (38.7)	0.453 (0.224-0.916)	0.038 ^a
Eczema questions				
Itchy rash lasting six months in life	2 (3.8)	28 (14.4)	0.225 (0.053-0.990)	0.057 ^a
Itchy rash in the past 12 months	1 (1.9)	24 (12.4)	0.134 (0.018-1.012)	0.044 ^a
Eczema ever	10 (18.5)	49 (25.3)	0.673 (0.315-1.437)	0.396 ^a

Abbreviation: CI = confidence interval

^aYate's correction of contingency.

^bFisher's exact test.

smoking) in T1D patients with and without atopy. The results reveal no significant difference in the prevalence of any of these risk factors between T1D patients with or without atopy symptoms (Table 4).

Discussion

In this study, the prevalence of atopic diseases was compared in children with T1D and an age-matched control group. The prevalence of asthmatic symptoms in the T1D group was clearly lower than in the control group. However, the overall prevalence of atopy was not significantly different in these two groups. Symptoms of allergic rhinitis, including "nose symptoms with itchy-watery eye in the past 12 months", and "hay fever or nasal allergy ever" were less prevalent in the T1D group.

Several studies published in past decades demonstrated an inverse relationship between the presence of

atopic disease and T1D [9-13]. Atopic diseases were rarely seen in patients with T1D in the past. However, these early studies didn't select conscientious reference groups. Hermansson et al [14] reported a lower probability of atopy in children with T1D, and their siblings as well, compared with control subjects. Douek et al [15] found that a significantly lower proportion of children with T1D had symptoms of asthma compared with siblings or control subjects. The frequency and severity of symptoms were also significantly lower among the children with T1D. In addition, the EURODIAB (European Diabetes) Substudy 2 Study Group [16] found a decreased prevalence of atopic diseases, particularly asthma, in children with T1D compared with age-matched controls.

However, not all studies support this association. Since the 1980s, in some reports, the prevalence of atopic diseases in T1D children was similar to that of the

Table 3. Prevalence of asthma, rhinitis and eczema in children with type 1 diabetes mellitus (T1D) and controls

	T1D (n = 54) No. (%)	Controls (n = 194) No. (%)	Odds ratio (95% CI)	<i>p</i>
Any asthma symptom ^a	11 (20.4)	71 (36.6)	0.443 (0.215-0.914)	0.036 ^b
Any rhinitis symptom	28 (51.9)	101 (52.1)	0.992 (0.542-1.813)	0.978 ^b
Any eczema symptom	13 (24.1)	53 (27.3)	0.658 (0.330-1.318)	0.236 ^b
Any atopic symptom	37 (68.5)	148 (76.3)	0.676 (0.349-1.312)	0.246 ^b

Abbreviation: CI = confidence interval

^a*p*<0.05 (Fisher's exact test).

^bYate's correction of contingency.

Table 4. Risk factors in patients with type 1 diabetes mellitus (T1D) with atopy versus those without atopy

	T1D with atopy (n = 57) No. (%)	Odds ratio (95% CI)	<i>p</i>
Breast-feeding	19 (33.3)	2.571 (0.966-6.846)	0.054
Pets	14 (24.6)	1.506 (0.679-3.339)	0.907
Family smoking	31 (54.4)	0.947 (0.380-2.359)	0.313

Abbreviation: CI = confidence interval

general public [17,18]. Stromberg et al [19], in a study of 81 children with T1D and 72 control subjects, did not find a significant difference in the prevalence of atopic disease as defined by history, clinical features, skin prick test results, serum immunoglobulin E (IgE), or circulating IgE antibodies to allergens. Recently, Caffarelli et al did not succeed in demonstrating an inverse relation between Th1- and Th2-mediated diseases in children with IgE sensitization or an atopic genetic predisposition [20].

Notably, the presence of T1D does not completely inhibit atopic diseases. In patients with multiple sclerosis, 4% had symptoms of atopic disease [21]. O'Driscoll et al also concluded that patients with rheumatoid arthritis had a normal prevalence of atopic diseases and there was no evidence that allergic factors contributed to the arthritis of the rheumatoid arthritis patients [22]. Therefore, the presence of a Th1-mediated disease was only one of the factors which influenced the presentation of atopic symptoms. The variation of atopy symptoms in T1D patients may be explained by the influence of some factors such as (passive) smoking, having pets and ever breast-feeding. These factors are known to influence atopic symptoms [23-25].

In our study, we compared data that aimed to determine whether occurrence of atopic diseases in T1D patients was associated with (passive) smoking, pet exposure, or breast feeding. We found no obvious association between atopy and these factors in T1D patients.

Several previous studies have discussed the relationship between environmental factors and atopic symptoms in Taiwan [26,27]. Taichung is a highly urbanized environment, and Taiwan has a subtropical climate, with high humidity and temperature; all of these conditions are associated with the development of atopic symptoms. In a study from Finland, Poysa et al found that the prevalence of atopy was highest in southern Finland, the most urbanized area of this country, and was lowest in eastern Finland, the most agrarian area

[28]. Li and Hsu concluded that dampness in the home was very common in the subtropical region studied, and that home dampness was a strong predictor of respiratory symptoms [29]. Also, increased temperature (up to 30°C) and increased relative humidity favor the growth of dust mites [30], a major risk factor in the development of atopic symptoms [31]. Thus, it is likely that these environmental factors played a role in increasing the likelihood of atopic symptoms in the Taiwanese children in our study.

To the best of our knowledge, this is the first report to show a significant inverse relationship between T1D and some atopic symptoms in Taiwan. Nevertheless, we have identified two major limitations in the study. First, our hospital is a single medical center in central Taiwan. More hospitals are needed to participate in this research for completeness. Second, the role of family history, known to be linked to atopic symptoms, should be considered in studies of atopic disease risk.

Our study shows a lower prevalence of atopic disease in children with T1D compared with the control group, especially asthma. The results are consistent with a recent study from Europe reporting that children with diabetes had fewer symptoms of asthma compared with the background population [16]. This suggests that the occurrence of Th1-mediated diseases may protect against the development of Th2-mediated atopic disease. Furthermore, investigation of the role of environmental factors is important in advancing understanding of the occurrence of atopic diseases in T1D patients.

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