

Influence of the T_H1/T_H2 Paradigm: The Prevalence of Asthma and Allergic Diseases in Patients with Type 1 Diabetes in the United States

SHIH-WEN HUANG, M.D.,¹ and JEFF HITCHCOCK²

ABSTRACT

To test the T_H1/T_H2 paradigm, we determined the prevalence of asthma and allergic disorders (T_H2-driven diseases) in children with type 1 diabetes (a T_H1-driven disease) in the United States. The survey was conducted using an online survey (www.childrenwithdiabetes.com). In 3 months, we enrolled a total of 403 children with diabetes (under the age of 18) and 480 nonaffected siblings (also under the age of 18) for statistical analysis. We compared the prevalence of allergic diseases in patients with type 1 diabetes to that of their nonaffected siblings and used the general population as a control. Our results were as follows for children with/without diabetes/general population respectively: bronchial asthma, 18 of 403 (4.4%) versus 35 of 480 (7.2%) versus 1025 of 10,904 (9.4%); allergic rhinitis, 57 of 403 (14.1%) versus 101 of 480 (21.0%) versus 1203 of 4295 (28.0%); atopic dermatitis, 22 of 403 (5.5%) versus 39 of 480 (8.1%) versus 113 of 1126 (10.0%). The difference between the patients and the controls was significant for all three diseases ($p = 0.0033$ to 0.0055), but not between the patients and their nonaffected siblings or between the siblings and the controls. The lower prevalence of asthma and allergic disorders in children with type 1 diabetes was also confirmed in patients in the United States, suggesting that T_H1- and T_H2-driven diseases can be mutually exclusive (although this is not absolute). Genetic and environmental factors are equally important in modulating T_H1 and T_H2 responses. (*Pediatr Asthma Allergy Immunol* 2002; 15[4]:195–199.)

INTRODUCTION

THE IMMUNE RESPONSE begins with innate immunity and is fostered by adaptive immunity, which can be divided into the selective response carried by either T_H1 cells or T_H2 cells.^(1,2) T_H1 cells secrete interleukin (IL)-2 (IL-2) and interferon- γ , while T_H2 cells secrete IL-4, IL-5, IL-9, and IL-13. The genetic propensity and presentation of antigen(s) at an early age help to modify the immune response that favors T_H1 or T_H2 dominance, which is further sustained by the presence and interaction of these respective proin-

¹Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida.

²Founder of the Children with Diabetes web site (www.childrenwithdiabetes.com), West Chester, Ohio.

A portion of the study was presented at the 57th Annual Meeting of the American Academy of Allergy, Asthma and Immunology on March 20, 2001, in New Orleans, in the minisymposium entitled, "Hot Topics in ARRD."

flammatory cytokines and anti-inflammatory cytokines such as IL-10. The immunologic responses enhanced or modified by these cytokines may be clinically divided and designated as T_H1 - or T_H2 -driven disorders. On one end of the spectrum of inflammatory diseases, T_H1 -driven diseases include organ-targeted autoimmune diseases such as multiple sclerosis and type 1 diabetes. On the other end, T_H2 -driven diseases include a host of allergic diseases in which IgE plays a major role in clinical manifestation. With what appears to be a polarity between the two inflammatory responses, we would like to propose a hypothesis that T_H1 - and T_H2 -driven diseases may not coexist and may even be mutually exclusive in the same individual.

We addressed this issue by determining the prevalence of allergic disorders in patients with type 1 diabetes. A review of the literature indicated that nearly 70 years ago, Swern⁽³⁾ observed a low prevalence of diabetes among patients with allergies. However, in that study, neither the type of diabetes nor the mechanism of the exclusion was proposed. Recently, two studies reported the prevalence of asthma in patients with type 1 diabetes in European countries.^(4,5) Although these reports supported Swern's observations, one was focused only on the prevalence of asthma in a specific region in the United Kingdom, while the other mentioned only the overall prevalence of asthma and allergic diseases from unknown locations in European countries. Therefore, whether the geographic factor plays a role remains uncertain. We proposed to examine not only the prevalence of asthma, but also the prevalence of allergic rhinitis and atopic dermatitis, the two most common allergic disorders, in patients with type 1 diabetes. We then compared the results with those of siblings without diabetes and the general population in the United States.

METHODS

We conducted an online survey of parents of patients with type 1 diabetes. Twenty-four questions were posted on a website, www.childrenswithdiabetes.com. The inclusion criteria were that the patient: (1) had been diagnosed with type 1 diabetes by a physician; (2) was younger than 18 years; (3) was a U.S. citizen residing in this country; and (4) had been actively treated for diabetes.

The survey inquired about the presence of bronchial asthma (BA), allergic rhinitis (AR), and atopic dermatitis (AD). To ensure the accuracy of the reports, we only collected the following information for analysis: (1) a list of the clinical manifestations of each disorder; (2) the diagnosis by a physician; and (3) confirmation that the patients had received treatment. If there was any ambiguity in the responses, we dismissed that case from the study.

For a comparison of the prevalence of BA, AR, and AD, we used the data in the National Health and Nutritional Examination Survey (NHANES) III reported in 1997 to represent the prevalence in the general population. Our survey was started in 1999.

The χ^2 test was used for statistical analysis using Prism software, version 3.0 (GraphPad Software, San Diego, CA) to compare the prevalence of these diseases between the patient group and the controls.

RESULTS

Because the gender ratio in the group with diabetes and their siblings was almost even (male:female = 203:200 in the former and 253:227 in the latter group), we combined them for a final analysis. The average age of the siblings without diabetes was younger by 1.5 years. The prevalences of each of the allergic diseases are illustrated in Figure 1. When we compared the prevalence of each of the diseases among the three groups, we consistently found that the only significant difference was between the group with diabetes and the general population ($p = 0.001$ for BA; $p = 0.003$ for AR; $p = 0.006$ for AD). The prevalence of these diseases in siblings without diabetes was higher than that in the group with diabetes, but was lower than that in the general population (however, the differences were not significant). The odds ratio and 95% confidence interval in the diabetic group for BA, AR, and AD were 0.53 (0.34 ~ 0.83), 0.69 (0.54 ~ 0.88), and 0.52 (0.32 ~ 0.80), respectively.

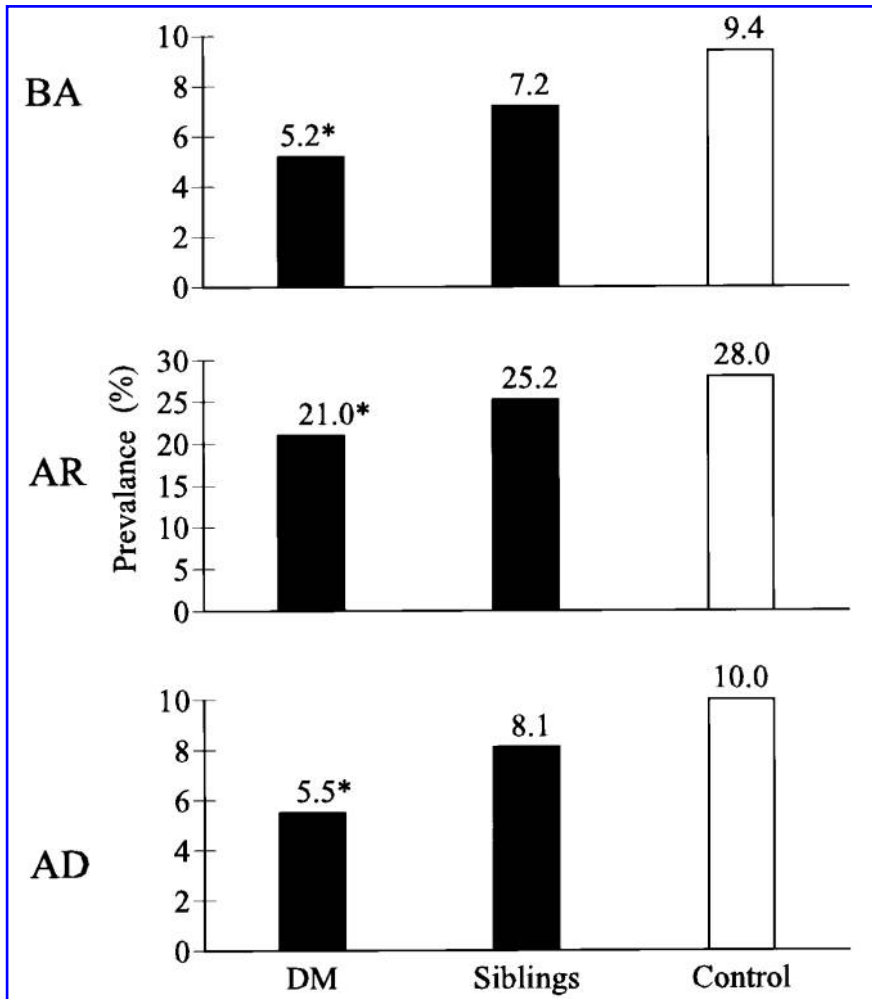


FIG. 1. Prevalence of bronchial asthma (BA), allergic rhinitis (AR), and atopic dermatitis (AD) in patients with type 1 diabetes (DM), their siblings without diabetes, and the general population (control). The only significant statistical difference* was found between the DM and the controls: BA ($p = 0.001$), AR ($p = 0.003$), AD ($p = 0.006$).

DISCUSSION

The findings of the current study support previous clinical observations⁽³⁾ and the European studies^(4,5) showing that the lower prevalence of BA in patients with type 1 diabetes, the organ-targeted autoimmune chronic inflammation in the islets of pancreas, were not coincidental. However, the mechanisms underlying the T_H1/T_H2 paradigm may be more complex than the interplay of the few cytokines that we mentioned in the introduction. For instance, we began to appreciate that the beginning of immune response caused by early life processes such as exposure to infectious agents, age, the manner of antigen presentation, and the site of antigen presentation may determine the gradual dominance of either the T_H1 or the T_H2 response. The recent report that early exposure to cat antigen can produce an immunoglobulin (Ig)-G and IgG4 antibody response without sensitization or risk of asthma illustrates another possible influence.⁽⁶⁾ Also, the possible existence of T-regulatory cells has recently been proposed to help explain the unexpected outcome of the interplay between T_H1 and T_H2 cells.⁽⁷⁾ Overall, however, it appears that when the dominant immunologic response is enhanced by cytokines of T_H1 cells such as IL-2 and interferon- γ , this diminishes the effect of cytokines from T_H2 cells in the same host. The end result is that in patients with T_H1-driven diseases (such as type 1 diabetes), T_H2-driven diseases such as childhood asthma are usually not found.

This hypothesis is further supported by our findings that the incidence of both AR and AD is lower in patients with type 1 diabetes.

Some questions still remain about this discordance between T_H1 - and T_H2 -driven diseases occurring in the same individual. For example, after type 1 diabetes is well established, the target of the T_H1 -driven response will eventually destroy all of the insulin-producing islet cells in the pancreas. If the T_H1 -driven response is diminished after this complete destruction, then the T_H1/T_H2 balance may tilt toward T_H2 . Furthermore, then, allergic asthma or allergic disorders should increase in diabetic patients. This could be the reason that some patients with diabetes have asthma or allergic disorders. Also, during the early stage of diabetes, it has been reported that both T_H1 and T_H2 cytokines may be decreased in the same individual.⁽⁸⁾ Further study is needed to understand whether other factors, especially environmental factors, might play a role in the net outcome of the T_H1/T_H2 paradigm.

Comparing the data collected from NHANES to those of our online survey of patients with diabetes will not be enough to answer these questions. To determine the time of onset of type 1 diabetes and the onset of asthma or allergic disorders in each individual patient requires a larger prospective, clinically well-controlled population study.

There are potentially two implications of these findings that may help to develop a new modality of treatment of asthma or allergic diseases. First, the cross-inhibition of T_H2 -driven disease with opposite cytokines, especially interferon- γ , may lessen the severity or suppress the development of asthma or allergic diseases. Indeed, there are some early reports showing that recombinant interferon- γ suppresses AD in humans⁽⁹⁻¹¹⁾ and reverses airway hyperactivity in animals.⁽¹²⁾ Other antiprolinflammatory cytokine therapies using anti-IL-4 or anti-IL-5 for the lessening of allergic inflammation are on the horizon as well. The cross-inhibition of T_H1 disease with IL-4 is certainly possible. However, as stated above, in order to preserve the targeted organ of T_H1 disease, the intervention must be early enough. Otherwise, the value of such intervention could become somewhat unpredictable.

Second, these findings support the concept of developing a new form of immunotherapy in which an antigen is bonded to a CpG motif oligodeoxynucleotide. It is anticipated that this new antigen will invoke the T_H1 response selectively, for example, with the release of interferon- γ to lessen the severity of T_H2 -driven diseases. Reports using cedar pollen allergens⁽¹³⁾ and bee venom phospholipase A_2 sequence-carrying DNA plasmids⁽¹⁴⁾ as antigens have produced some promising results in animals. More clinical trials using these modified antigens in humans are anticipated in the future.

Obviously, the interplay of cytokines in the early stages of T_H1 - or T_H2 -driven diseases is more complex than we realized. However, the clinical outcome that we observed in these surveys suggests that the severity of T_H2 -driven diseases may be lessened or the diseases can even be prevented if we have a better understanding of the sequence of the complicated immunologic process. We also recognize that our study was not conducted in a prospective manner and in a parallel fashion with a control population. Therefore, the accuracy on data collection could be questioned. It should be noted, however, that Szczeklik et al⁽¹⁵⁾ reported earlier a metabolic study in which they concluded that a shift favoring the economic use of insulin rather than catecholamine in asthmatic patients may explain why they are unlikely to develop type 1 diabetes. This observation suggests that an unexplored connection between the immune response and the catecholamine response protects asthmatic patients from developing type 1 diabetes.

Our finding that the prevalence of asthma and allergic disorders is higher in children without diabetes than in their siblings with diabetes but lower than that in the general population in the United States for all three diseases suggests that genetics and environment are equally important in modulating the T_H1 and T_H2 immune responses.

REFERENCES

1. Del Prete G, De Carli M, Mastromauro C, Biagiotti R, Macchia D, Falagiani P, Ricci M, Romagnani S. Purified protein derivative of *Mycobacterium tuberculosis* and excretory-secretory antigen(s) of *Toxocara canis* expand *in vitro* human T cells with stable and opposite type 1 T helper or type 2 T helper profile of cytokine production. *J Clin Invest* 1991; 88:346-350.

2. Romagnani S. Human T_H1 and T_H2: Doubt no more. *Immunol Today* 1991; 12:256–257.
3. Swern N. Incidence of diabetes mellitus in asthmatic patients. *J Allergy* 1932; 2:375–378.
4. The EUROPEAN ACE Substudy, 2 Study Group. Decreased prevalence of atopy in diabetic children. *Diabetologia* 1998; 41(Suppl 1):A 22.
5. Diuek IF, Leech NJ, Gillmor HA, Bingley PJ, Gale EAM. Children with type 1 diabetes and their unaffected siblings have fewer symptoms of asthma. *Lancet* 2000; 353:1850.
6. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified T_H2 response in children exposed to cat allergen: A population-based cross-sectional study. *Lancet* 2001; 357:752–756.
7. Rook GAW. Clean living increases more than just atopic disease. *Immunol Today* 2000; 21:249.
8. Halminen M, Simell O, Knip M, Ilonen J. Cytokine expression is unstimulated PBMC of children with type 1 diabetes and subjects positive for diabetes-associated autoantibody. *Scand J Immunol* 2001; 53:510–513.
9. Stevens SR, Hanifen JM, Hamilton T, Tofte ST, Cooper KD. Long-term effectiveness and safety of recombinant human interferon gamma therapy for atopic dermatitis despite unchanged serum IgE levels. *Arch Dermatol* 1988; 134:799–804.
10. Noh GW, Lee KY. Blood eosinophils and serum IgE as predictors for prognosis of interferon-gamma therapy in atopic dermatitis. *Allergy* 1998; 53:1202–1207.
11. Ellis CN, Stevens SR, Blok BK, Taylor RS, Cooper KD. Interferon-gamma therapy reduces blood leukocyte levels in patients with atopic dermatitis. *Clin Immunol* 1999; 92:49–55.
12. Huang TJ, MacAry PA, Eynott P, Moussavi A, Daniel KC, Askenase PW. Allergen-specific T_H1 cells counteract effluent T_H2 cell-dependent bronchial hyperresponsiveness and eosinophil inflammation partly via IFN- γ . *J Immunol* 2001; 166:207–217.
13. Kohama Y, Akizuki O, Hagihara K, Yamada E, Yamamoto H. Immunostimulatory oligodeoxynucleotide-induced T_H1 immune response and inhibition of IgE antibody production to cedar pollen allergens in mice. *J Allergy Clin Immunol* 1999; 103:1231–1238.
14. Jilek S, Barbey C, Spertini F, Cortes. Antigen-independent suppression of the allergic immune response to bee venom phospholipase A₂ by DNA vaccination in CBA/J mice. *J Immunol* 2001; 166:3612–3621.
15. Szczeklik A, Pieton R, Sieradzki J. Alteration in both insulin release and its hypo-glycemic effects in atopic bronchial asthma. *J Allergy Clin Immunol* 1980; 66:424–427.

Address reprint requests to:

Shih-Wen Huang, M.D.

Department of Pediatrics

Box 100296

University of Florida College of Medicine

Gainesville, FL 32610

E-mail: huangsw@peds.ufl.edu

This article has been cited by:

1. Nadine Taleb, Pierre Bou Khalil, Mira S. Zantout, Pierre Zalloua, Sami T. Azar. 2009. Prevalence of asthmatic symptoms in Lebanese patients with type 1 diabetes and their unaffected siblings compared to age-matched controls. *Acta Diabetologica* . [[CrossRef](#)]
2. 2003. LiteratureWatchLiteratureWatch. *Pediatric Asthma, Allergy Immunology* **16**:1, 63-66. [[Citation](#)] [[PDF](#)] [[PDF Plus](#)]