# Predisposition to Atopic Symptoms to Inhaled Antigens May Protect From Childhood Type 1 Diabetes

PETRI S. MATTILA, MD[1]
JUSSI TARKKANEN, MD[2]
HARRI SAXEN, MD[3]
JANNE PITKÄNIEMI, MSC[4]
MARJATTA KARVONEN, PHD[4]
JAAKKO TUOMILEHTO, MD[4,5]
THE CHILDHOOD DIABETES IN FINLAND (DIME) STUDY GROUP

**OBJECTIVE** — To assess the inverse association between type 1 diabetes and asthma to establish whether environmental and/or genetic factors predisposing to asthma or to atopic symptoms to inhaled antigens protect from diabetes.

**RESEACH DESIGN AND METHODS** — Questionnaires were returned by 306 probands with childhood type 1 diabetes, their 506 nonaffected siblings, and 406 age- and sex-matched unaffected population control subjects. The main outcome measures were self-reported physician-diagnosed asthma and atopic symptoms to animal dust and pollen.

**RESULTS** — Risk of diabetes was inversely associated with asthma (odds ratio 0.49 [95% CI 0.24–1.00]), allergy to animal dust (0.67 [0.45–0.99]), and to a lesser degree to pollen (0.74 [0.51–1.07]) when the probands were compared with the population control subjects. Among the children of the families of an affected proband, the risk of diabetes appeared to be inversely associated with asthma (0.54 [0.27–1.09]) but not with allergy to animal dust (0.99 [0.66–1.47]) nor allergy to pollen (0.88 [0.62–1.27]).

**CONCLUSIONS** — The frequency of asthma and atopic symptoms to some inhaled antigens is decreased in individuals with childhood type 1 diabetes. Factors predisposing to atopic symptoms to inhaled antigens may protect from childhood type 1 diabetes.

*Diabetes Care* 25:865–868, 2002

Childhood type 1 diabetes results from immune-mediated destruction of pancreatic insulin-producing cells (1). The immune response leading to this destruction is thought to be of the Th1 type (2), whereas the type of immune response in asthma and atopy is thought to be of the Th2 type (3). This has raised questions as to whether a decreased risk of asthma and atopy among children with type 1 diabetes is due to the reciprocal effect of Th1 and Th2 immune responses (4,5). This would further suggest that factors predisposing to either diabetes or asthma might result in a decrease in the frequency of asthma in diabetes. On the other hand, it has been suggested that the diabetic phenotype per se with hyperglycemia and endocrine abnormality may contribute to an inverse association between asthma and diabetes (6). The above reports indicate an inverse association between the risk of asthma and childhood type 1 diabetes. The occurrence of these diseases have, however, been reported to have a positive association when the incidences of asthma and type 1 diabetes have been compared between different countries in an ecological analysis (7). This suggests that there are also factors that increase the risk of both asthma and type 1 diabetes.

To assess the association between diabetes and asthma, the frequency of asthma and atopy was evaluated among individuals with childhood type 1 diabetes and among sex- and age-matched unaffected population control subjects. To establish whether genetic and/or environmental factors predisposing to asthma and atopy contribute to the association between asthma and diabetes, the siblings of the diabetic individuals were also studied. In addition, since results of our preliminary study showed that adenoidectomy at an early age was strongly associated with asthma (P.S.M., J.T., H.S., J.P., M.K., J.T., unpublished observations), adenoidectomy status was included in the analysis as an independent variable.

## RESEARCH DESIGN AND METHODS

— A questionnaire was sent to 819 probands with type 1 childhood diabetes (aged ≤14 years at the time of diagnosis), their 1,082 siblings, and 819 age- and sex-matched unaffected population control subjects in 1998. They had previously served as a study cohort in another study on diabetes epidemiology (8). The ages of the probands and unaffected population control subjects ranged from 10 to 27 years at the time the questionnaire was mailed. Altogether, 347 (42%) probands, 620 (57%) siblings of the probands, and 483 (59%) unaffected population control subjects returned completed questionnaires. At the time of the survey, the mean age of the probands was 18.4 years (ranging from 11 to 26 years), and the mean age of the siblings and control subjects was 19.2 years (ranging from 2 to 43 years) and 18.3 years (ranging from 10 to 27 years), respectively. In the analysis, those sib-

From the [1]Department of Otorhinolaryngology, Helsinki University Central Hospital, Helsinki, Finland; the [2]Department of Pathology, Haartman Institute, Helsinki University Central Hospital, Helsinki, Finland; the [3]Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland; the [4]National Public Health Institute, Diabetes and Genetic Epidemiology Unit, Helsinki, Finland; and the [5]Department of Public Health, University of Helsinki, Helsinki, Finland.

Members of the Childhood Diabetes in Finland (DiMe) Study Group are listed in reference 8.

Address correspondence and reprint requests to Petri S. Mattila, Department of Otorhinolaryngology, Helsinki University Central Hospital, Haartmaninkatu 4 E, FIN-00290 Helsinki, Finland. E-mail: petri.mattila@hus.fi.

Received for publication 18 October 2001 and accepted in revised form 16 February 2002.

**Abbreviations:** OR, odds ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 1—*Frequency of asthma and allergy to animal dust and pollen by adenoidectomy status among probands with type 1 diabetes, among nondiabetic population control subjects, and among unaffected siblings of the probands***

| | Diabetic probands | Nondiabetic population control subjects | | Unaffected siblings of the probands | |
|---|---|---|---|---|---|
| | Frequency* | Frequency | OR (95% CI)† | Frequency | OR (95% CI)‡ |
| All participants | | | | | |
| Asthma | 4.1 (361) | 6.7 (478) | 0.60 (0.32–1.13) | 6.8 (592) | 0.60 (0.33–1.10) |
| Animal dust allergy | 17.7 (350) | 21.4 (453) | 0.79 (0.55–1.13) | 16.9 (562) | 1.06 (0.74–1.50) |
| Pollen allergy | 21.5 (349) | 25.4 (456) | 0.80 (0.58–1.12) | 22.9 (564) | 0.92 (0.67–1.27) |
| Participants who had not undergone adenoidectomy | | | | | |
| Asthma | 3.4 (265) | 5.8 (359) | 0.57 (0.26–1.26) | 6.1 (442) | 0.54 (0.25–1.17) |
| Animal dust allergy | 14.8 (256) | 19.9 (341) | 0.70 (0.45–1.08) | 15.4 (422) | 0.96 (0.62–1.47) |
| Pollen allergy | 18.4 (255) | 24.7 (344) | 0.69 (0.46–1.03) | 21.8 (421) | 0.81 (0.54–1.19) |
| Participants who had undergone adenoidectomy before the age of 4 years | | | | | |
| Asthma | 5 (41) | 15 (47) | 0.29 (0.06–1.50) | 8 (64) | 0.61 (0.11–3.28) |
| Animal dust allergy | 23 (39) | 36 (44) | 0.53 (0.20–1.38) | 20 (61) | 1.23 (0.46–3.25) |
| Pollen allergy | 31 (39) | 29 (45) | 1.09 (0.43–2.79) | 22 (60) | 0.61 (0.64–4.02) |

Frequency data are % (*n*). *The numbers of the individuals of whom the relevant information was available are given in parenthesis, †OR and 95% CI of the contribution of asthma and allergy to animal dust and pollen to the risk of diabetes when the nondiabetic population control subjects were used as the reference, ‡same as above, but the unaffected siblings of the probands were used as the reference.

lings ($n = 19$) who had been diagnosed to have diabetes later than the proband, as verified by the records of the National Diabetes Registry, were included in the analysis as a proband.

The following questions on asthma, allergy to inhaled antigens, and adenoidectomy were asked: *1*) Have you been diagnosed to have asthma by a physician? *2*) At what age was your asthma diagnosed? *3*) Have you ever been diagnosed to have any allergy to the following airborne allergens: *a*) animal dust (dog, cat, horse, etc.) and *b*) pollen? *4*) Have your adenoids been removed (adenoidectomy)? and *5*) If adenoidectomy was performed, at what age was it done?

The questions were followed by multiple-choice answer fields including "no," "yes," and "do not know" choices in applicable places. The questionnaire also included a picture with explanatory text showing the anatomical location of the adenoids and tonsils to help the respondent understand the questions concerning adenoidectomy. The survey was approved by the Ethical Review Committee of the Finnish National Health Institute, Helsinki. Multivariate logistic regression analysis was performed to evaluate independent risk factors for diabetes.

**RESULTS** — The frequencies of asthma and allergy to the inhaled antigens, animal dust and pollen, among the probands, siblings, and unaffected population control subjects are given in Table 1. In addition, the frequencies of asthma and allergy to inhaled antigens are given separately for those study subjects who had undergone adenoidectomy before the age of 4 years and for those who had not undergone adenoidectomy (Table 1). The frequency of asthma and allergy was somewhat lower among the probands than among the unaffected control population. It was higher among those who had undergone adenoidectomy at an early age (Table 1).

To test risk factors for diabetes (dependent variable), an analysis was performed, first, among the probands as compared with the population control subjects and, second, among the probands as compared with the unaffected siblings, with asthma, sex, and adenoidectomy status entered as independent variables (Table 2). Another set of analyses was carried out, with sex, allergy to animal dust, and adenoidectomy status entered as independent variables. Yet another set of analyses was carried out, with sex, allergy to pollen, and adenoidectomy status entered as independent variables (Table 2). These three sets of analyses, each with three independent variables, were performed instead of one with all of the five variables (i.e., asthma, allergy to animal dust, allergy to pollen, sex, and adenoidectomy status). Asthma and allergy to animal dust were very strongly associated with each other (odds ratio [OR] 17.6) as well as asthma and allergy to pollen (8.9) and allergy to pollen and animal dust (36.2).

The analysis revealed that the risk of diabetes was inversely associated with allergy to animal dust when the probands were compared with the population control subjects (OR 0.67 [95% CI] 0.45–0.99, $P = 0.0450$) (Table 2) but not when the probands were compared with their siblings (0.99 [0.66–1.47]) (Table 2). On the other hand, the risk of diabetes was inversely associated with asthma when the probands were compared with the population control subjects (0.49 [0.24–1.00], $P = 0.0505$) (Table 2), and there was also a tendency for the diabetic probands to have a lower frequency of asthma than their unaffected siblings (0.54 [0.27–1.09], $P = 0.0862$) (Table 2).

The analysis showed an association between sex and diabetes when the probands were compared with their siblings, because the female siblings of the probands returned the questionnaire more often than the male ones (data not shown).

**CONCLUSIONS** — In the current study, the diagnosis of diabetes or no di-

**Table 2 —*Factors associated with the risk of childhood type 1 diabetes***

| Independent variables | Risk of type 1 diabetes | |
|---|---|---|
| | Probands versus population control subjects | Probands versus their siblings |
| Analyses set 1 | | |
| Asthma (yes/no) | 0.49 (0.24–1.00) | 0.54 (0.27–1.09) |
| Sex (M/F) | 1.06 (0.78–1.42) | 1.38 (1.04–1.84)* |
| Adenoidectomy (yes†/no) | 1.23 (0.78–1.94) | 1.09 (0.71–1.66) |
| *n* | 712 | 811 |
| Analyses set 2 | | |
| Animal dust allergy (yes/no) | 0.67 (0.45–0.99)* | 0.99 (0.66–1.47) |
| Sex (M/F) | 1.07 (0.79–1.46) | 1.38 (1.00–1.79) |
| Adenoidectomy (yes†/no) | 1.25 (0.78–1.99) | 1.06 (0.69–1.64) |
| *n* | 680 | 777 |
| Analyses set 3 | | |
| Pollen allergy (yes/no) | 0.74 (0.51–1.07) | 0.88 (0.62–1.27) |
| Sex (M/F) | 1.03 (0.76–1.39) | 1.38 (1.03–1.84)* |
| Adenoidectomy (yes†/no) | 1.20 (0.76–1.90) | 1.09 (0.70–1.68) |
| *n* | 683 | 774 |

Data are OR (95% CI) of the risk of type 1 diabetes. *$P < 0.05$. †Before the age of 4 years.

abetes was verified by the records of the National Diabetes Registry (8), which allowed an objective diagnosis. The frequency of asthma was evaluated by the question "Have you been diagnosed as having asthma by a physician?" Such an approach presumably results in a rather specific and sensitive diagnosis of asthma because self-reported physician-diagnosed asthma has been shown to correlate well with objective findings of asthma diagnosis (9,10). Furthermore, the diagnosis of asthma by physicians in Finland is made by uniform criteria because it entitles the patient to a reimbursement for asthma medication granted by the Finnish Social Insurance Institute. The criteria for asthma diagnosis are based on the recommendations of the American Thoracic Society.

Self-reported atopic symptoms may not always have a good correlation with objective findings of atopy, such as skin-prick tests or serum allergen specific or total IgE (9). Although symptoms of respiratory allergy have been shown to have a better correlation with serum allergen specific or total IgE than symptoms of atopic dermatitis (11), the evaluation of self-reported symptoms of allergy to inhaled antigens is restricted in that it may reflect a broader range of hypersensitivity reactions that may not completely parallel atopy confirmed by skin-prick tests or specific IgE measurements. We attempted to minimize this bias in the self-reported atopic symptoms in the present survey by asking the participants whether they had ever been "diagnosed" as having an allergy to animal dust or pollen.

We have previously found that adenoidectomy at early age is strongly associated with asthma (P.S.M., J.T., H.S., J.P., M.K., J.T., unpublished observations). This could be seen primarily among the unaffected control population. To account for the possible confounding effect of adenoidectomy status, it was entered as an independent variable in the multiple logistic regression analysis. The analysis revealed that diabetes was inversely associated with asthma independently of adenoidectomy status or sex.

Our observation of the decreased frequency of asthma and respiratory allergic symptoms among diabetic children is in keeping with the results of the two previous reports (4,5). In a multicenter study involving eight European centers with 1,028 diabetic and 2,744 nondiabetic individuals, the risk of self-reported asthma (OR 0.66 [95% CI 0.49–0.90]) and self-reported eczema or allergic rhinoconjunctivitis (0.79 [0.64–0.97]) was decreased among children with type 1 diabetes (5). In another study involving 157 diabetic children, 173 siblings of the diabetic children, and 2,324 control children, the history of ever wheezing was decreased among diabetic subjects as compared with the control subjects (0.36 [0.25–0.52]) (4). However, there was no difference between the groups in response to the question "Have you ever been told that you have asthma?" (4), which is in contrast to the results of the above multicenter study (5) and to our results.

In this survey, complete information was available from 306 probands, 506 unaffected siblings, and 406 unaffected control subjects. Thus far, this study is the largest on asthma and diabetes that also involves the unaffected siblings. As compared with the unaffected population control subjects, many, though not all, unaffected siblings of the probands presumably have genetic predisposition to type 1 diabetes and/or have been exposed to environmental factors that may trigger type 1 diabetes. Therefore, the analysis using the unaffected siblings as a reference enabled us to indirectly estimate the contribution of these risk factors. The analysis revealed that although the risk of diabetes was inversely associated with asthma when the probands were compared with the population control subjects, it also appeared to be decreased when the probands were compared with their unaffected siblings. However, the risk of diabetes was inversely associated with atopic symptoms to animal dust when the probands were compared with the population control subjects but not when the probands were compared with their siblings; moreover, the OR between the probands and their siblings was close to 1. This suggests that the probands and their unaffected siblings apparently share a genetic and/or environmental background that reduces the risk of developing animal dust allergy.

The results suggest that the risk of type 1 diabetes is inversely associated with asthma and atopic symptoms to inhaled antigens. Factors predisposing to atopic symptoms to inhaled antigens may protect against type 1 diabetes.

**Acknowledgments**— This work received financial support from the Paulo Foundation, Helsinki, Finland; Research Funds of Helsinki University Central Hospital; and the Academy of Finland grants 3837 and 46558.

**References**

1. Atkinson MA, Maclaren NK: The pathogenesis of insulin-dependent diabetes mellitus. *N Engl J Med* 331:1428–1436, 1994
2. Solimena M, De Camille P: From Th1 to Th2: diabetes immunotherapy shifts gears. *Nat Med* 2:1311–1312, 1996
3. Del Prete G: Human Th1 and Th2 lymphocytes: their role in the pathophysiology of atopy. *Allergy* 47:450–455, 1992
4. Douek IF, Leech NJ, Gillmor HA, Bingley PJ, Gale EA: Children with type-1 diabetes and their unaffected siblings have fewer symptoms of asthma. *Lancet* 353: 1850, 1999
5. Dahlqvist G, Patterson C, Soltész G: Decreased prevalence of atopic diseases in children with diabetes. The EURODIAB Substudy 2 Study Group. *J Pediatrics* 137: 470–474, 2000
6. Vianna EO, Garcia-Leme J: Allergen-induced airway inflammation in rats: role of insulin. *Am J Resp Crit Care Med* 151:809–814, 1995
7. Stene LC, Nafstad P: Relation between occurrence of type 1 diabetes and asthma. *Lancet* 357:607–608, 2001
8. Tuomilehto J, Lounamaa R, Tuomilehto-Wolf E, Reunanen A, Virtala E, Kaprio EA, Akerblom HK: Epidemiology of childhood diabetes mellitus in Finland: background of a nationwide study of type 1 (insulin-dependent) diabetes mellitus. The Childhood Diabetes in Finland (DiMe) Study Group. *Diabetologia* 35:70–76, 1992
9. Kauppi P, Laitinen LA, Laitinen H, Kere J, Laitinen T: Verification of self-reported asthma and allergy in subjects and their family members volunteering for gene mapping studies. *Resp Med* 92:1281–1288, 1998
10. Barnes KC, Freidhoff LR, Horowitz EM, Mathias RA, Mulkern DM, Bonacum JT, Goldman MH, Polito AJ, Saini SS, Marsh DG, Beaty TH, Togias A: Physician-derived asthma diagnoses made on the basis of questionnaire data are in good agreement with interview-based diagnoses and are not affected by objective tests. *J Allergy Clin Immun* 104:791–796, 1999
11. Haahtela T, Jaakonmäki I: Relationship of allergen-specific IgE antibodies, skin prick tests and allergic disorders in unselected adolescents. *Allergy* 36:251–256, 1981