K. Engkilde · T. Menné · J. D. Johansen

Inverse relationship between allergic contact dermatitis and type 1 diabetes mellitus: a retrospective clinic-based study

Received: 2 December 2005 / Accepted: 14 December 2005 / Published online: 21 February 2006
© Springer-Verlag 2006

Abstract *Aims/hypothesis:* Contact allergy (CA) is a disease induced and maintained by environmental factors, which mainly has a Th2 pattern in its chronic form. Environmental factors play a major role in CA, while genetic factors are of minor importance. Type 1 diabetes is an autoimmune disease of the islets of Langerhans, which has a Th1 cytokine pattern and in which modulators of risk are both genetic and environmental. To investigate whether environmental exposure to chemicals leading to CA could influence the risk of type 1 diabetes, we conducted a retrospective clinic-based study of patients subjected to diagnostic patch testing of CA. *Methods:* We undertook a retrospective clinic-based study of 13,315 patients who were patch-tested between 1985 and 2003, and linked it with the Danish National Patient Registry containing diabetic mellitus discharge diagnoses from 1987 to 2003. The 13,315 patch-tested patients gave rise to 4,848 CA patients. Using logistic regression, we calculated odds ratios for persons with CA of having type 1 diabetes. *Results:* Type 1 diabetes was diagnosed in 229 of the patch-tested patients. CA patients had a reduced risk of having type 1 diabetes, with an odds ratio 0.62 (95% CI 0.46–0.86). After adjusting for sex and age, the odds ratio was 0.63 (95% CI 0.47–0.86). *Conclusions/interpretation:* An inverse relationship between CA and type 1 diabetes was found. Thus there may be a protective effect of having CA in relation to the risk of type 1 diabetes, or vice versa type 1 diabetes may lead to tolerance rather than hypersensitivity. Alternatively, these two diseases may share common genetic factors, although at present these are unknown.

Keywords Allergic contact dermatitis · Contact allergy · Logistic regression · Type 1 diabetes mellitus

Abbreviations CA: contact allergy · DM: diabetes mellitus · ICD: International Classification of Diseases · NKT cells: natural killer T cells

Introduction

Contact allergy (CA) is a delayed type IV reaction involving T lymphocytes. It is caused by skin contact with substances of small molecular weight in the environment. Once a patient is sensitised to an allergen, re-exposure will result in allergic contact dermatitis, which is an inflammatory skin disease characterised by erythema and infiltration at the site of contact. CA is common in the general population, where 15 to 20% are sensitised to substances in the environment [1]. CA is rare among infants but increases rapidly in adolescents, with 15% of schoolchildren aged 12 to 16 years having a CA to one or more common environmental allergens, close to the level established in adults [2]. Individual predispositions to CA exist; however, the total number of sensitised individuals in a population has mainly to do with environmental factors [3], while genetic factors only play a minor role [4–6].

T cells and Langerhans cells are of importance in the induction and elicitation of the allergic response. Moreover, it was recently established that the invariant natural killer T cell (NKT) plays a pivotal role in CA [7, 8].

Type 1 diabetes mellitus is also a chronic disease, and is the result of an autoimmune Th1 cell-mediated destruction of the beta cells. The rise in the incidence of type 1 diabetes mellitus in recent decades points to hitherto unknown environmental factors [9].

Studies have found NKT cell numbers to be reduced in type 1 diabetes mellitus [10, 11], while activation of these cells by α -galactosylceramide prevents the onset of type 1 diabetes mellitus [12, 13]. The relationship between NKT cells and CA seems to be different from the relationship between NKT cells and type 1 diabetes mellitus, since NKT

K. Engkilde (✉) · T. Menné · J. D. Johansen
National Allergy Research Centre, Department of Dermatology,
Gentofte Hospital, University of Copenhagen,
DK-2820, Copenhagen, Denmark
e-mail: kaaeng02@gentoftehosp.kbhamt.dk
Tel.: +45-39978267
Fax: +45-39777118

cells seem to be necessary for elicitation of CA [8], while NKT cells suppress the development of type 1 diabetes mellitus.

The aim of the present study was to investigate the association between CA and type 1 diabetes mellitus, and thus whether environmental exposure to chemicals leading to CA might influence the risk of type 1 diabetes mellitus.

Subjects, materials and methods

From 1985 to 2003, a total of 13,315 patients (4,818 males and 8,497 females), were patch-tested at the Department of Dermatology, Gentofte Hospital, University of Copenhagen, Denmark. The patients were referred to the department because of chronic dermatitis. The outcome of the patch test together with information regarding sex and date of birth were recorded in the allergy database. All patients were patch-tested with the European Standard Series recommended at the time of testing. The European Standard Series contains the most important contact allergens in the environment for continental Europe. Patch testing was performed, according to international standards, on the upper back using Trolab allergens (Hermal, Reinbek, Germany) and Finn chambers for occlusion (Epitest, Tuusula, Finland). Occlusion time was 48 h and the patches were read on days 2, 3 and 7 according to international criteria from the International Contact Dermatitis Research Group [14, 15]. A positive allergic reaction was defined as at least erythema and infiltration in the test area. Of the 13,315 people tested, 4,848 had been tested at least once with a positive response to one of the test allergens.

At birth, or in the case of immigration, all Danish citizens are given a unique and personal identifier number, a CPR number, which is used for identification in databases. This enables linking of individuals' data over time and between databases.

Using the CPR number, the allergy database was linked with the Danish National Patient Registry, which contains the codes of diagnoses from the International Classification of Diseases 8th and 10th revisions (ICD8 and ICD10). The Danish National Patient Registry contains information on all hospital admissions, discharge diagnoses and operations performed since 1977, and furthermore contains outpatient contacts from 1 January 1995. Patients with the ICD8 code 249 or the ICD10 code E10 were categorised as having type 1 diabetes mellitus. From 1977 to 1993 the Danish National Patient Registry used the ICD8, and since 1994

the ICD10 has been used. The standard WHO version of the ICD8 contains only one diabetic code (250); however, the Danish National Patient Registry introduced the code 249 in January 1987 to account for type 1 diabetes mellitus. We can therefore identify type 1 diabetes mellitus patients treated from 1987 to 1994 in hospital, and from 1995 to 2003 we can also identify type 1 diabetes mellitus patients treated as outpatients.

Age was calculated as the age at the first positive patch test; if there was no positive patch test, the age at the first patch test was used. The patients were stratified into five age groups: 0–15, 16–30, 31–50, 51–70 and >70 years of age.

The resulting data file was analysed using logistic regression with the patch test outcome as the dependent variable and type 1 diabetes mellitus as the independent variable, and controlled for sex and age. Odds ratios with 95% CIs were estimated using logistic regression. All data analysis was done using SPSS version 12 (SPSS, Chicago, IL, USA).

Results

The 13,315 patients were patch-tested between 1985 and 2003; of these, 229 had an ICD code for type 1 diabetes mellitus (ICD8 249 or ICD10 E10). There were more females than males in the registry, and the number of females with a positive patch test was also higher than males (42.2 vs 26.3%). The age (defined as the age at the first positive patch test or if there where no positive patch test, the age at the first patch test) spanned from 6 to 99 years with a median of 47 years. Some of the patient categories can be found in Table 1.

An inverse association was found between CA and type 1 diabetes mellitus. The odds ratio for a person with CA of having type 1 diabetes mellitus was 0.62 (95% CI 0.46–0.83); when adjusted for sex and age, the odds ratio was 0.63 (95% CI 0.47–0.86). The result of the logistic regression can also be found in Table 2.

Discussion

An inverse relationship between CA, a type IV immunological reaction, and type 1 diabetes mellitus, an autoimmune disease, was found by record linking two databases: one of allergy and one of patient discharge diagnoses. Such a study has never been performed before and was only

Table 1 Overview of patient contact allergy categories in the allergy database

	Negative patch test (n=8,467)						Positive patch test (n=4,848)					
	Age group (years)						Age group (years)					
	0–15	16–30	31–50	51–70	>70	Total	0–15	16–30	31–50	51–70	>70	Total
Type 1 DM	0	12	39	80	38	169	0	4	17	28	11	60
No type 1 DM	166	1,866	2,766	2,359	1,141	8,298	36	866	1,808	1,421	657	4,788

DM, Diabetes mellitus

Table 2 Results from the logistic regressions with CA as the response variable and type 1 diabetes mellitus as the independent variable

	<i>p</i>	Odds ratio	95% CI of odds ratio
Type 1 DM	0.001	0.62	0.46–0.83
Type 1 DM adjusted for sex and age	0.003	0.63	0.47–0.86

There is an inverse relationship between CA and type 1 DM
DM, Diabetes mellitus

possible due to the collection of large patient populations and the unique identifier system in Denmark, which makes a linkage possible between such registers. The inverse relationship may lead to new theories and insight into disease mechanisms.

We identified cases of type 1 diabetes mellitus from discharge diagnoses from the Danish National Patient Registry for the period 1987 to 2003. The Danish National Patient Registry does not contain outpatient contacts until 1 January 1995, which means that patients with a milder course of type 1 diabetes mellitus may have escaped registration in the Registry until 1995. However, the period from 1987 to 1993 has previously been evaluated with respect to type 1 diabetes mellitus by Nielsen et al. [16], who found the specificity of the diagnoses to be 96.3% and the completeness to be 91%. In the period from 1987 to 1993 the ICD8 was used and we expect that the introduction of ICD10 in 1994 has not decreased the specificity and completeness of the registry. We therefore anticipate that most type 1 diabetes mellitus patients are accounted for. Additionally the prevalence of type 1 diabetes mellitus in our dataset is relatively high, which further indicated that we did account for most type 1 diabetes mellitus cases. The prevalence in our data is even higher than in most studies on childhood-onset type 1 diabetes mellitus; these studies, however, often focused on younger individuals.

Supporting our high number of type 1 diabetes mellitus patients is the article by Mølbak et al. 1994 [17], who found a high incidence of type 1 diabetes mellitus in Denmark, even in the age group above 30 years.

The patients with contact dermatitis entered the database because of referral to a university clinic, generally because of chronic dermatitis. Patch testing classified the patients in groups with and without CA (a positive patch test). Those with CA had decreased risk of type 1 diabetes mellitus independently of age and sex. A sampling bias because the investigation was based on hospital material would have led to a positive and not a negative association.

Even though population-based studies are often preferable to patient-based studies by virtue of unbiased estimation of prevalence and risk, when evaluating risk factors for CA they have limited power [18]. CA is not associated with an increased death rate, which could have interfered with the data. Any medical treatment of the two conditions is unlikely to introduce bias. Most of the CA

patients had been treated intermittently with topical steroids and only a minority with systemic immunosuppressants. This type of treatment is unlikely to have increased or decreased the risk of type 1 diabetes mellitus. None of the patients in the allergy database had been referred because of dermatitis reaction at the injection site, which otherwise could have induced a selection bias. The high median age of 47 years of the analysed patients means that most of those who during their lifetime will develop CA and/or type 1 diabetes mellitus have already done so at the time of allergy testing (patch testing).

There are more females than males in the allergy database and there are also more females than males with a positive patch test, which is in accord with the literature [3].

Several studies have evaluated the potential relationship between atopic dermatitis and type 1 diabetes mellitus. The outcome is not uniform, but most studies point to a negative association [19–22]. Those studies, however, deal with children and recorded atopic illnesses prior to the development of diabetes mellitus. One study found the association only to be significant for the older age group (10–14 years) [22] and one study only found an inverse association if atopic dermatitis was diagnosed before onset of type 1 diabetes mellitus [23]. Atopic dermatitis is defined as a clinical syndrome, and is not based on a specific immunological event, in contrast to CA, which might explain this variation.

CA has not previously been investigated with respect to autoimmune diseases, probably because CA has not been regarded as a Th2-dominated illness [24]. However, recent studies have found that in patients with long-lasting dermatitis, as in the present patient material, a Th2 response is anticipated [25, 26]. In this study, we found an inverse relationship between CA and type 1 diabetes mellitus. This finding could lead to the hypothesis that CA is an environmentally acquired factor modulating the risk of developing type 1 diabetes mellitus. Alternatively the inverse relationship could be explained by genetic factor or environmental determinates; however, at present genetic factors are not considered to play a major role in CA and there are no known shared environmental factors.

CD1d-restricted NKT cells have shown interesting abilities in regulating the immune system in both a suppressing and an enhancing direction [27]. Therefore, the NKT cell has been studied in the pathogenesis of a number of autoimmune disease, including type 1 diabetes mellitus. The nonobese diabetic mouse has been found to be numerically and functionally deficient in NKT cells [10]. Furthermore a study of identical twins discordant for type 1 diabetes mellitus also showed differences in gene expression of NKT cells [11]. The NKT cells respond to α -galactosylceramide, a glycolipid, in the context of CD1d. Treatment of nonobese diabetic mice with α -galactosylceramide has been found to protect against diabetes [12, 13, 28]; a review of NKT cells in relation to type 1 diabetes mellitus is found in [29].

In an animal model of CA, Campos et al. [7] found an increased level of NKT cells in the liver after induction of

CA. Furthermore, recent studies have shown that NKT cells are important in the elicitation of CA [7, 8].

We have also investigated the relationship between CA and type 2 diabetes mellitus, but found no association (data not shown). This can be explained by the fact that type 2 diabetes mellitus is not a Th1-mediated autoimmune disease. However, patients with type 2 diabetes mellitus are not followed in the same way through the hospital system as patients with type 1 diabetes mellitus, since most are treated by a general practitioner, which probably leads to an underassessment of type 2 diabetes mellitus patients.

In conclusion, we found an inverse relationship between CA and type 1 diabetes mellitus. This association might be related to shared genetic factors or common environmental determinates; however, genetics is generally thought to be a minor factor in the development of CA. Another possibility is that development of CA influences the immune system, so that the risk of developing type 1 diabetes mellitus is reduced, or vice versa.

CA has not previously been found to have an association with autoimmune diseases, which is why this study may stimulate research into the immunological interaction between environmental skin exposure and autoimmune diseases.

Acknowledgement This study was financed by a grant from the National Board of Health.

References

- Martin SF (2004) T lymphocyte-mediated immune responses to chemical haptens and metal ions: implications for allergic and autoimmune disease. *Int Arch Allergy Immunol* 134:186–198
- Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE (2002) Contact allergy and allergic contact dermatitis in adolescents: prevalence measures and associations. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). *Acta DermVenereol* 82:352–358
- Agner T, Menné T (2006) Individual predisposition to irritant and allergic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P (eds) *Contact dermatitis*, 4th edn. Springer, Berlin and Heidelberg, pp 127–134
- Bryld LE, Hindsberger C, Kyvik KO, Agner T, Menne T (2004) Genetic factors in nickel allergy evaluated in a population-based female twin sample. *J Invest Dermatol* 123:1025–1029
- Karvonen J, Silvennoinen-Kassinen S, Ilonen J, Jakkula H, Tiilikainen A (1984) HLA antigens in nickel allergy. *Ann Clin Res* 16:211–212
- Westphal GA, Schnuch A, Moessner R et al (2003) Cytokine gene polymorphisms in allergic contact dermatitis. *Contact Dermatitis* 48:93–98
- Campos RA, Szczepanik M, Itakura A et al (2003) Cutaneous immunization rapidly activates liver invariant V α 14 NKT cells stimulating B-1 B cells to initiate T cell recruitment for elicitation of contact sensitivity. *J Exp Med* 198:1785–1796
- Nieuwenhuis EE, Gillessen S, Scheper RJ et al (2005) CD1d and CD1d-restricted iNKT-cells play a pivotal role in contact hypersensitivity. *Exp Dermatol* 14:250–258
- Onkamo P, Vaananen S, Karvonen M, Tuomilehto J (1999) Worldwide increase in incidence of type I diabetes-the analysis of the data on published incidence trends. *Diabetologia* 42:1395–1403
- Hammond KJ, Pellicci DG, Poulton LD et al (2001) CD1d-restricted NKT cells: an interstrain comparison. *J Immunol* 167:1164–1173
- Wilson SB, Kent SC, Horton HF et al (2000) Multiple differences in gene expression in regulatory V α 24J α Q T cells from identical twins discordant for type I diabetes. *Proc Natl Acad Sci USA* 97:7411–7416
- Hong S, Wilson MT, Serizawa I et al (2001) The natural killer T-cell ligand α -galactosylceramide prevents autoimmune diabetes in non-obese diabetic mice. *Nat Med* 7:1052–1056
- Sharif S, Arreaza GA, Zucker P et al (2001) Activation of natural killer T cells by α -galactosylceramide treatment prevents the onset and recurrence of autoimmune type 1 diabetes. *Nat Med* 7:1057–1062
- Wilkinson DS, Fregert S, Magnusson B et al (1970) Terminology of contact dermatitis. *Acta DermVenereol* 50:287–292
- Wahlberg J, Lindberg M (2006) Patch testing. In: Frosch PJ, Menné T, Lepoittevin J-P (eds) *Contact dermatitis*, 4th edn. Springer, Berlin, Heidelberg and New York, pp 365–390
- Nielsen GL, Sorensen HT, Pedersen AB, Sabroe S (1996) Analyses of data quality in registries concerning diabetes mellitus—a comparison between a population based hospital discharge and an insulin prescription registry. *J Med Syst* 20:1–10
- Mølbak AG, Christau B, Marner B, Borch-Johnsen K, Nerup J (1994) Incidence of insulin-dependent diabetes mellitus in age groups over 30 years in Denmark. *Diabet Med* 11:650–655
- Uter W, Pfahlerberg A, Gefeller O, Geier J, Schnuch A (2003) Risk factors for contact allergy to nickel-results of a multifactorial analysis. *Contact Dermatitis* 48:33–38
- Stene LC, Joner G (2004) Atopic disorders and risk of childhood-onset type 1 diabetes in individuals. *Clin Exp Allergy* 34:201–206
- Rosenbauer J, Herzig P, Giani G (2003) Atopic eczema in early childhood could be protective against type 1 diabetes. *Diabetologia* 46:784–788
- Cardwell CR, Shields MD, Carson DJ, Patterson CC (2003) A meta-analysis of the association between childhood type 1 diabetes and atopic disease. *Diabetes Care* 26:2568–2574
- Dahlquist G, Patterson C, Soltesz C et al (2000) Decreased prevalence of atopic diseases in children with diabetes. The EURODIAB Substudy 2 Study Group. *J Pediatr* 137:470–474
- Olesen AB, Juul S, Birkebaek N, Thestrup-Pedersen K (2001) Association between atopic dermatitis and insulin-dependent diabetes mellitus: a case-control study. *Lancet* 357:1749–1752
- Kimber I, Basketter DA, Gerberick GF, Dearman RJ (2002) Allergic contact dermatitis. *Int Immunopharmacol* 2:201–211
- Borg L, Christensen JM, Kristiansen J, Nielsen NH, Menne T, Poulsen LK (2000) Nickel-induced cytokine production from mononuclear cells in nickel-sensitive individuals and controls. Cytokine profiles in nickel-sensitive individuals with nickel allergy-related hand eczema before and after nickel challenge. *Arch Dermatol Res* 292:285–291
- Kitagaki H, Ono N, Hayakawa K, Kitazawa T, Watanabe K, Shiohara T (1997) Repeated elicitation of contact hypersensitivity induces a shift in cutaneous cytokine milieu from a T helper cell type 1 to a T helper cell type 2 profile. *J Immunol* 159:2484–2491
- Godfrey DI, Kronenberg M (2004) Going both ways: immune regulation via CD1d-dependent NKT cells. *J Clin Invest* 114:1379–1388
- Naumov YN, Bahjat KS, Gausling R et al (2001) Activation of CD1d-restricted T cells protects NOD mice from developing diabetes by regulating dendritic cell subsets. *Proc Natl Acad Sci USA* 98:13838–13843
- Hussain S, Wagner M, Ly D, Delovitch TL (2005) Role of regulatory invariant CD1d-restricted natural killer T-cells in protection against type 1 diabetes. *Immunol Res* 31:177–188