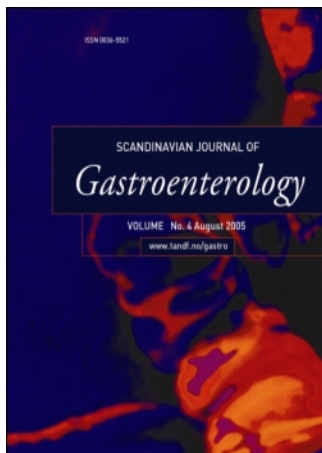


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Inflammatory bowel disease in relation to contact allergy: A patient-based study

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ORIGINAL ARTICLE

**Inflammatory bowel disease in relation to contact allergy:
A patient-based study**

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Objective. Inflammatory bowel disease (IBD) has previously been investigated with relation to allergic conditions; however, diverging results were found and there are only a few small studies focusing on delayed hypersensitivity. The aim of this study was to investigate whether there was an association between contact allergy (CA), which is a type IV hypersensitivity reaction of the skin, and IBD. **Material and methods.** A database consisting of a cohort of 13,315 patients, patch tested between 1985 and 2003, was linked with the Danish National Patient Registry using a unique personal identifier number. The patients were patch tested at a dermatology department with a long history of research in CA. By record linking with the Danish National Patient Registry, patients were identified who had either an International Classification of Disease (ICD) code for Crohn's disease (CD) or an ICD code for ulcerative colitis (UC) diagnosis. Using logistic regression, with the result of the patch test as the dependent variable, we calculated the odds ratios for IBD, CD and UC, adjusted for gender and age. **Results.** An inverse association between CA and IBD was found, odds ratio adjusted for age and gender 0.71 (CI 95% 0.53–0.94), which is mainly the result of an inverse association between CA and CD, odds ratio adjusted for age and gender 0.42 (CI 95% 0.23–0.76). **Conclusions.** The association found between CA and IBD might be related to shared genetic factors or common environmental determinates. It may also be that having either disease result in skewness of the immune system might lead to an inverse disease association.

Key Words: *Allergic contact dermatitis, contact allergy, Crohn disease, patch tests, ulcerative colitis*

Introduction

Contact allergy (CA) is a disease caused by skin contact with substances in the environment of small molecular weight. CA is a delayed-type hypersensitivity reaction, following a T-cell-mediated response. The T-cell response consists of both a Th-1 and a Th-2 response [1], but it may verge more toward a Th-2 response in chronic eczema following CA [2,3], which may be directed toward reducing a harmful Th-1 response, since CD4⁺ T cells can have a down-regulatory effect [4].

CA develops in two phases, which are defined operationally as the induction (sensitization) and elicitation phase. In the induction phase, skin contact with a contact allergen of a sufficient dose causes activation and expansion of contact allergen-specific T lymphocytes. The elicitation phase begins upon

contact with the allergen in question and results in clinical manifestation of allergic contact dermatitis (ACD). ACD is characterized by erythema and infiltration at the skin site of contact.

The main cells of importance in CA are, besides the T cells, the Langerhans cells and dermal dendritic cells, and the natural killer T (NKT) cell may also play a pivotal role [5].

CA is rare among infants but common in adolescents: 15% of children aged 12–16 years have CA to one or more allergens [6], which is similar to the level in the adult population [7]. Risk factors for CA are mostly related to environmental exposure, while genetic factors seemingly play only a minor role [8–11]; accordingly, CA is considered a disease mainly driven by the environment.

Inflammatory bowel disease (IBD) is an idiopathic and chronic intestinal inflammation. The two main clinical entities of IBD are Crohn's disease (CD) and

ulcerative colitis (UC). Both are chronic relapsing inflammatory conditions of the gastrointestinal tract.

The generally accepted notion is that the mucosa of patients with CD is dominated by CD4⁺ T cells with a Th-1 phenotype, while the mucosa of patients with UC is dominated by an atypical Th-2 phenotype [12–14].

Susceptibility to IBD is influenced by genetic predisposition, especially in CD where the concordance rate for monozygotic twins is relatively high, whereas the concordance rate for UC is low [15–17]. Nevertheless, since the concordance rate is well below 100%, non-genetic factors, primarily environmental or luminal, may be required to trigger IBD in a genetically susceptible host.

To investigate the relation between IBD and CA, we studied a large cohort of patients tested for CA in a university department of dermatology.

Material and methods

From 1985 to 2003, 13,315 patients (4818 M, 8497 F) were patch tested at the Department of Dermatology, Gentofte Hospital, University of Copenhagen, Denmark. Patch testing is the international standard test that is used to diagnose CA. Patients were typically referred to the department because of relapsing or chronic dermatitis. The outcome of the patch test, gender 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; this series contains the most important contact allergens in the environment for the European continent. 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 the international criteria from the International Contact Dermatitis Research Group (ICDRG) [18,19]. A positive allergic reaction was defined as at least homogeneous erythema and infiltration in the test area. The database has information on the test result for each of the days, but in the present study a binary variable was constructed; a positive test on any of the days to any of the allergens of the European Standard Series at any test time rendered the patient positive. Of the 13,315 people tested, 4848 had a positive response, at least once, to one of the tested allergens.

At birth, or on immigration, all Danish residents are given a unique and personal identification number (a CPR number) which is used for identification in databases. This enables linkage of individual data over time and between databases.

Using the unique identifier (CPR), 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 revision (ICD8 and ICD10). The Danish National Patient Registry contains information on all hospital admissions, discharge diagnoses and operations performed since 1977, and outpatient contacts from 1 January 1995. Patients with the ICD8 code 56301 or the ICD10 code DK50 were categorized as having CD, while patients with the ICD8 code 56319 or the ICD10 code DK51 were categorized as having UC. Patients with either an ICD code for CD or UC were categorized as having IBD. From 1977 to 1993 the Danish National Patient Registry used the ICD8, and since 1994 the ICD10 has been used [20].

Age was calculated as 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.

The resulting data file was analysed using logistic regression, with the patch test outcome as the dependent variable and IBD or CD or UC as the independent variable, and controlled for gender and age. Odds ratios with 95% confidence intervals (CIs) were estimated using logistic regression. All data analyses were done using SPSS version 12 (SPSS Inc., Chicago, Ill., USA).

Results

Of the 13,315 patients, 225 had at least one ICD8 or ICD10 code for IBD (ICD8 56301 or 56319; ICD10 DE50 or DE51); of these, 34 had diagnoses of both UC and CD, and of the remaining 191 patients, 73 had a CD diagnosis and 118 had a UC diagnosis (Table I).

The age span was 6–99 years (median 47 years): for patients with a UC diagnosis only, the age span was 15–91 years (median 49 years); for the CD group, 9–86 years (median 43 years); and for those with an ICD code for both CD and UC, the span was 13–73 years (median 42.5 years).

There were more females than males in the registry, and also more females with a positive patch test than males (42.2% versus 26.3%).

When adjusting for gender and age group, patients with an IBD diagnosis had an odds ratio of 0.71 of having CA (CI 95% 0.53–0.95).

The IBD diagnosis was further split into three groups: patients with a CD diagnosis only, patients with a UC diagnosis only and patients with both a CD and a UC diagnosis. Only the group with a CD diagnosis had a significant association with CA

Table I. Overview of the number of patients in the CD and UC categories.

Number of patients in the various groups		Negative patch test		Positive patch test		Total
		Male	Female	Male	Female	
Both a CD and a UC diagnosis	CD & UC	8	15	3	8	34
CD diagnosis only	CD	26	33	0	14	73
UC diagnosis only	UC	32	46	14	26	118
No diagnosis for IBD	No IBD	3487	4820	1248	3535	13090

Abbreviations: CD = Crohn's disease; UC = ulcerative colitis; IBD = inflammatory bowel disease.

($p=0.004$). The odds ratio for a patient with a CD diagnosis only of having a positive patch test was 0.42 (CI 95% 0.23–0.76).

Discussion

We found an inverse association between CA and IBD, which was mainly due to an inverse association between CA and CD. The odds ratio for CD adjusted for age and gender was 0.42 (CI 95% 0.23–0.76) (Table II). This investigation is unique: as it is based on a large cohort of patients followed over 19 years at a university department of dermatology, and the record linking used is possible only in Denmark, where a unique personal identifier system has long been used in all registers.

The study concerned patients referred to the dermatology department for patch testing. CA is generally more common among females [8], and this explains the gender difference in the database. This difference is reflected among the patients with a CD or UC diagnosis (Table I). In Denmark, CD is more common among females, but this is not the case for UC [21,22].

In two studies the estimated prevalence of UC and CD was found to be, respectively, 160 and 54 per 100,000 inhabitants [21,23]. However, more recently, a study covering the period from 1981 to 1992 found an increasing incidence of CD [24], which would result in a higher prevalence. Furthermore, outpatients were first included in the Danish National Patient Registry in 1995.

The study was based on discharge diagnoses, which may vary in quality between hospitals and over time; however, this potential bias would be

similar for CD and UC, while only the odds ratio for CD is significant. The Danish National Patient Registry has been investigated previously in the county of Northern Jutland, and here the completeness of the Danish National Patient Registry using the pathology system as a reference standard was 94% for both CD and UC, and the validity was 97% and 90%, respectively [25]. The present study largely included patients from the county of Copenhagen, which is an area where patients with IBD have been registered over a long period [21,23], and the validity and completeness of the Danish National Patient Registry in this area is therefore at least on the same level as those of Northern Jutland.

A sampling bias caused by the investigation being based on hospital material would have led to a positive and not a negative association. Although 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 [26]. CA is not associated with an increased death rate, which could have interfered with the data. Most of the CA patients had been treated intermittently with topical steroids, and only a minority with systemic immunosuppressive drugs. This treatment is unlikely to have influenced the risk of IBD.

A possible confounding factor in our study could be smoking, as smoking increases the risk of CD, but has a protective effect in UC [27]. Studies have found that smoking might increase the risk of CA [28], but this common risk factor for CA and CD would have resulted in a positive rather than a negative association as found in this study. It might, however, have reduced a positive association between CA and UC.

Table II. Results from the logistic regression with CA as the response variable and inflammatory bowel disease, CD or UC as the independent variables.

Association between contact allergy and IBD	Adjusted for	<i>p</i> -value	Odds ratio	CI 95%
IBD		0.019	0.71	0.53–0.94
IBD	Age and gender	0.02	0.71	0.53–0.95
Both a CD and a UC diagnosis	Age and gender	0.64	0.83	0.40–1.73
CD	Age and gender	0.004	0.42	0.23–0.76
UC	Age and gender	0.53	0.88	0.60–1.30

Abbreviations: CA = contact allergy; CD = Crohn's disease; UC = ulcerative colitis; IBD = inflammatory bowel disease.

Another possible confounder is medical treatment of IBD with immunosuppressants, e.g. azathioprine or prednisolone; however, if this treatment had an effect on the risk of CA, it would most likely be the same for both UC and CD. Medical therapy with anti-tumour necrosis factor alpha (TNF- α) is presumably a confounder, since migration of Langerhans cells is inhibited by anti-TNF- α treatment [29]; mice deficient in the TNF- α gene have an impaired contact hypersensitivity reaction [30]. Treatment of CD with anti-TNF- α might therefore interfere with the patch test result. However, infliximab was not introduced in Denmark until late 1999 [31], and is therefore unlikely to be a problem in this study. Furthermore, patients with a down-regulated elicitation response would most likely not have been patch tested, and therefore would not be included in the database.

IBD has previously been studied in relation to allergy; the results were divergent [32–35], and only a few and relatively small studies focused on delayed hypersensitivity [36,37]. Triantafyllidis et al. [36] found that patients with CD had a reduced delayed hypersensitivity response to microbial antigens in the multi-test [36], while D'Arienzo et al. found no statistical differences between CA in a small cohort of patients with UC and controls [37].

In our study we found an inverse association between CA and IBD, which was mainly caused by the inverse association between CA and CD. CA is generally considered to be a Th-1 disease; however, studies have suggested that in chronic CA dermatitis, the cytokine milieu is more of a Th-2 profile [2]. The patients in our study mostly had chronic or relapsing contact dermatitis and could therefore have had a Th-2 cytokine profile, which could explain the inverse association to CD.

A possible relation between CA and IBD could be the natural killer T (NKT) cells. In 2004, Fuss et al. found non-classical CD1d restricted NKT cells involved in oxazolone-induced colitis, an animal model for UC [38]. In the dextran sulphate sodium (DSS)-induced colitis mouse model, it has been shown that administration of both α -galactosylceramide and OCH improved the colitis [39,40], which indicates that activation of the NKT cell improves resolution from this induced colitis model. The number of circulating NKT cells is reduced in patients with CD or UC [41], but the frequency and function of NKT cells from different organs might be unrelated [42] and the number in blood may therefore not be relevant. Nieuwenhuis et al. found that in oxazolone-induced contact hypersensitivity, CD1d-restricted NKT cells play a pivotal role [5]. Campos et al. found that the level of NKT cells in the liver increased after induction of CA [43]. Seemingly, the level of NKT cells is inversed in CA and IBD.

Using the same cohort, we previously investigated the relation between CA and type 1 diabetes and found an inverse association [44]. This and the previous study both point to an inverse association between CA and a Th-1-driven disease.

In conclusion we found an inverse relation between CA and IBD in the context of CD. This association might be related to shared genetic factors or common environmental determinates. However, genetic factors are generally thought to be a minor determinant in developing CA. Another possibility is that development of CA influences the immune system, thus reducing the risk of developing CD.

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