Inverse Association between Rheumatoid Arthritis and Contact Allergy

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Contact allergy (CA) is a delayed type IV hypersensitivity reaction caused by excessive cutaneous exposure to low-weight molecules (haptens or contact allergens), such as nickel, fragrances and preservatives. CA is traditionally diagnosed by patch-testing, a standardized skin test. In the 1950s Epstein & Jessar (1) showed that patients with rheumatoid arthritis (RA) displayed diminished susceptibility to developing contact sensitization. Since then, it has been reported that patients with RA have reduced delayed cutaneous hypersensitivity response when evaluated with a multi-test skin testing device (2), but have a normal inflammatory response towards the experimental allergen 2,4-dinitrochlorobenzene (DNCB) (3). Thus, the possible association between CA and RA remains unclear.

We have previously observed an inverse association between CA and prevalent autoimmune diseases (4–6). We investigate here whether an inverse association exists between CA and RA.

MATERIALS AND METHODS

At birth, or on immigration, Danish residents are given a unique and personal identifier number (CPR), which can be used for identification in databases. Using the CPR number, we linked a database containing patch-test results from dermatitis patients, tested with the European baseline series between 1985 and 2003 at Gentofte Hospital, with the Danish National Patient Registry (DNPR). The DNPR contains discharge diagnoses from 1977, and outpatient contacts are included from 1995. The DNPR is coded according to the International Classification of Diseases; version 8 (ICD8) between 1977 and 1993, and version 10 (ICD10) from 1994. An individual with one of the ICD8 codes: 71219, 71239, 71259 or one of the ICD10 codes: DM05, DM06 (except DM061, adult-onset Still's disease) were considered to have RA.

Age was defined as the age at first positive patch-test reaction. If there was no positive patch-test reaction, age was defined as the age at first patch-test procedure. Age was then stratified into five age groups: <30, 30–41, 42–52, 53–65, and >65 years. After linkage and stratification into age groups, data were analysed by logistic regression analysis, with CA as the dependent variable, and RA, sex and age group as the independent variables.

RESULTS

A total of 13,642 patients (36.3% male) were patch-tested from 1985 to 2003. A total of 35.8% of the patients had at least one positive patch-test reaction to at least one allergen at one of the reading days (day 2, 3 or 5/7 after application). Of individuals with positive patch-test reactions, 26.4% were men. After linkage with the DNPR, 352 patients (24.1% male) were identified as having RA. Of these 352 patients, 118 (20.3% male) had a positive patch-test reaction. When adjustments were made for age group and sex, RA was found to be inversely associated with CA (odds ratio (OR)=0.78; 95% confidence interval (CI)=0.62–0.98) (Table I).

DISCUSSION

We found an inverse association between RA and CA. The study is based on a large validated database and register, and the analysis is adjusted for the strongest confounders for CA (sex and age). The result is in line with a clinical experimental study conducted by Epstein & Jessar (1), in which they sensitized RA patients and healthy controls and demonstrated a reduced sensitization frequency among RA patients compared with controls. Moreover, it has been shown that RA patients have impaired cell-mediated immunity (7), which might reduce skin reactivity.

An important aspect of studies such as the present one is the validity of the diagnosis code. A conservative estimate of the validity of the RA diagnoses in the DNPR, using the clinical case definition, have been made previously by Pedersen et al. (8), who found the validity to be approximately 59%. The validity in our study may even be higher, as we used more recent data. To increase the specificity of the RA diagnosis, as well as trying to investigate the relation to the severity of RA, we additionally performed a logistic regression in which at least two registrations of RA in the DNPR were required. Hence, the number of patients was reduced to 256, and the logistic regression analysis adjusted for sex and age became insignificant ($p = 0.097$), although it still gave an inverse trend (Table I).

A weakness of our study was that we could not adjust for the use of systemic immune therapy, which is known to reduce patch-test reactivity; however, most cases (73%) were registered in the patch-test database before the RA diagnosis in DNPR (median year gap = 4).

Table I. *Results of logistic regression analysis with contact allergy as the dependent, and rheumatoid arthritis (RA) as the independent variable, adjusted for sex and age*

RA	*p*-value	OR	95% CI
RA diagnosis	0.033	0.780	0.621–0.980
≥2 diagnoses	0.097	0.799	0.613–1.042

OR: odds ratio; 95% CI: 95% confidence interval.

The inverse association between CA and RA might be explained by a genetic predisposition in subjects who are on track to develop RA or who have already developed RA. Thus, the immune system in this subgroup of individuals may already be skewed in a direction that inhibits the development of CA and instead results in RA. It is well known that the anti-cyclic citrullinated peptide (CCP) antibody may be positive long before onset of RA in pre-disposed individuals. The opposing theory is that CA modulates the immune system and lowers the risk of RA. Mortz et al. (9) showed that CA is already prevalent in children and adolescents, and, furthermore, we have shown that CA can prevent the development of diabetes in the non-obese diabetic mouse, which is prone to develop diabetes type 1 (10).

There is, at present, no genetic component that could explain the inverse association between RA and CA, and environmental factors, such as smoking, are positively associated with both disorders and would therefore not affect the inverse association.

In conclusion, we found an inverse correlation between RA and CA. The causality and reasons for this are unclear; however, insights into the immunological background hold valuable information that may be targeted in the development of future treatments.

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