Shared Epitope and Anti-Cyclic Citrullinated Peptide Antibodies: Relationship with Age at Onset and Duration of Disease in Rheumatoid Arthritis

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Shared Epitope and Anti-Cyclic Citrullinated Peptide Antibodies: Relationship with Age at Onset and Duration of Disease in Rheumatoid Arthritis

To the Editor:

Rheumatoid arthritis (RA) is a complex disease with a strong immune inflammatory component. Recent progress in defining the role of genetic factors in RA has been remarkable. It has been proposed that the shared epitope (SE) is a primary genetic element of susceptibility. Citrullination is a post-translational protein modification that is accomplished by deimination of arginine by peptidyl-arginine deiminases. Interestingly, polymorphisms in one member of the family, PADI4, have been associated with RA in Asian populations, although this association could not be reproduced in Caucasian populations. An association has been described between the presence of the SE and anti-cyclic citrullinated peptide antibody (anti-CCP) levels, and of each variable with disease severity. Also, anti-CCP-positive has been reported to be immunogenetically distinct from anti-CCP-negative disease, with the former subgroup being primarily responsible for association and linkage to HLA-DRB1 SE.

In this cross-sectional study we aimed at analyzing whether the presence of the SE and anti-CCP caused an acceleration in disease development that could be reflected in an earlier age at onset. This acceleration might be considered a sign of a worse prognosis.

We analyzed 411 Spanish patients with RA (76% women) consecutively recruited from a single center, all meeting American College of Rheumatology criteria for RA. Patients’ mean age at disease onset was 51 ± 15 years, and median disease duration was 8 years (range 3–15); 58% of patients carried the SE (Lifecodes HLA-SSO kit; Terpenel-Diagnostics Ltd., Abingdon, UK). The following alleles were identified: DRB1*0101, *0102, *0401, *0404, *0405, *0408, *1001 or *1402. Fifty-four percent of patients presented anti-CCP antibodies (determined by ELISA with Immunocan Euro-Diagnostica assay; Euro-Diagnostica, Malmoe, Sweden; single testing) and 69% were rheumatoid factor (RF)-positive (all patients who had been RF-positive in just one analysis irrespective of when the analysis had been performed). Statistical analysis was performed with standard statistical software (Stata v 9.0). Normality was tested by skewness and kurtosis tests.

There was a high association between anti-CCP and SE: 68% of 222 anti-CCP-positive individuals were also positive for SE, and only 47% of 189 anti-CCP antibody-negative patients were SE-positive (p = 0.00002; odds ratio 2.39, 95% CI 1.60–3.56; Table 1). In both groups of patients (anti-CCP-positive and anti-CCP-negative), SE positivity was statistically higher than in healthy Spanish controls (32% of 595 individuals; OR 4.53, 95% CI 3.22–6.40 for anti-CCP-positive and OR 1.90, 95% CI 1.34–2.69 (anti-CCP-negative), SE positivity was statistically higher than in healthy Spanish controls (32% of 595 individuals; OR 4.53, 95% CI 3.22–6.40 for anti-CCP-positive and OR 1.90, 95% CI 1.34–2.69). In both groups of patients (anti-CCP-positive and anti-CCP-negative), SE positivity was statistically higher than in healthy Spanish controls (32% of 595 individuals; OR 4.53, 95% CI 3.22–6.40 for anti-CCP-positive and OR 1.90, 95% CI 1.34–2.69).

We analyzed whether disease duration was dependent on SE or presence of anti-CCP (positivity); only the presence of anti-CCP antibodies was associated with disease duration (p = 0.005). The presence of SE showed no statistically significant association with disease duration (p = 0.62; Table 2). In order to ascertain the relationship between SE, anti-CCP antibodies, age at onset, and disease duration, we performed a univariate analysis of variance test considering all these variables. As Table 1 shows, the trend for association (p = 0.07) observed between anti-CCP antibodies and age at onset disappeared when disease duration was taken into account (p = 0.52). Positivity for both factors (SE and anti-CCP antibodies) simultaneously was not associated with earlier age at onset, when adjusted by disease duration, even when compared with double-negative patients (p = 0.15). Therefore, our data suggest that association of anti-CCP with age at onset is secondary to disease duration.

It can be argued that, as a result of an inflammatory process, anti-CCP antibodies may appear not only before the first symptoms, as has been occasionally described, but also during the course of the disease. According to this idea, we have shown in our study that it is more probable to find anti-CCP antibodies after a long disease history. Indeed, our data suggest that an association exists between anti-CCP antibodies and disease duration (Table 2), but not primarily with age at onset (Table 1). These results are supported by reports that have described the acquisition of anti-CCP antibodies, resulting from an immune response. There are no studies analyzing the prevalence of anti-CCP antibodies during the whole course of the disease (anti-CCP antibodies have been a recent addition to the RA personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved. Downloaded from www.jrheum.org on June 20, 2017 - Published by The Journal of Rheumatology

Table 1. Statistical analysis of age at RA onset using parametric test.

<table>
<thead>
<tr>
<th>Age at Disease Onset</th>
<th>Bivariate p, β (95% CI)</th>
<th>Multivariate p, β (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE + 240 (59) 50 (± 17) 0.12, –2.46 (–5.58; 0.65) 0.16, –2.07 (–4.95; 0.81)*†</td>
<td></td>
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<tr>
<td>− 171 (41) 52 (± 14)</td>
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<tr>
<td>CCP + 222 (54) 50 (± 15) 0.07, –2.82 (–5.90; 0.26) 0.52, –0.93 (–3.81; 1.94)*†</td>
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<tr>
<td>− 189 (46) 53 (± 16)</td>
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<tr>
<td>SE/CCP double-positive 151 (37) 48 (± 14) 0.05, –4.01 (–8.12–0.10) 0.15, –2.7 (–6.35–0.95)*†</td>
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<tr>
<td>SE/CCP double-negative 100 (24) 53 (± 18)</td>
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<td>Duration of disease</td>
<td>&lt;10^–3, –0.76 (–0.92; –0.61)</td>
<td>&lt;10^–3, –0.75 (–0.90; –0.59)*</td>
</tr>
</tbody>
</table>

* Adjusted by sex. † Adjusted by duration of disease. SE: shared epitope; CCP: Citric citrullinated peptide.

Table 2. Statistical analysis of disease duration using Mann-Whitney U test.

<table>
<thead>
<tr>
<th>Disease Duration, Median yrs (interquartile range)</th>
<th>p</th>
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<tbody>
<tr>
<td>SE + 9 (4–15)</td>
<td>0.62</td>
</tr>
<tr>
<td>− 8 (3–15)</td>
<td></td>
</tr>
<tr>
<td>CCP + 10 (4–16)</td>
<td>0.005</td>
</tr>
<tr>
<td>− 7 (2–12)</td>
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</tbody>
</table>

SE: shared epitope; CCP: Citric citrullinated peptide.
diagnostic arsenal), but Rönnelid, et al. showed that during the first 5 years for anti-CCP-positive individuals, antibody levels remained fairly constant. Nonetheless, it is remarkable that 3 out of 119 anti-CCP-negative patients (2.5%; analyzed with the same anti-CCP assay) became positive after only 1 year of followup.

The fact that anti-CCP-negative patients have higher SE positivity than that found in our healthy control population (49% vs 32%) suggests that the SE contributes independently to RA development, even in absence of anti-CCP antibodies. We are aware that our hypothesis contrasts with current thinking on the role of the SE in RA pathogenesis, and further studies will be necessary to fully address this issue.

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