Letters to the Editors

Carbonic anhydrase auto-antibodies and sicca symptoms in primary Sjögren’s syndrome

Sirs.

Carbonic anhydrases (CAs) are key enzymes in the regulation of acid-base balance in the body, including the maintenance of salivary pH homeostasis (1). Patients with primary Sjögren’s syndrome (pSS) have been found to have elevated levels of autoantibodies against the cytosolic CA enzymes I and II (2), although they are not specific for pSS. In recent years, several new CA isoenzymes have been identified (1). We reported recently that pSS patients have higher titers of anti-CA I, anti-CA II, anti-CA VI and anti-CA VII antibodies compared with subjects presenting with sicca symptoms but not fulfilling the criteria for pSS (3). In particular, we observed that antibodies to CA II, VI, and XIII were associated with renal manifestations of pSS in that they correlated with urinary pH (3).

It has been shown in experimental mouse models that anti-CA II antibodies may cause both a lymphocytic interstitial nephritis and an autoimmune lymphocytic sialadenitis similar to those in pSS (4, 5), suggesting that the anti-CA II antibody might be a pathogenic factor in these processes. Therefore, we hypothesised that in addition to correlating with renal manifestations of pSS, antibodies to the more novel CAs might also have roles in the salivary and other sicca symptoms of pSS. We therefore analysed the relationships of anti-CA I, II, VI, VII and XIII antibodies, determined by ELISA tests as previously described (3), with the spectrum of sicca symptoms in 74 pSS patients (72 females and 2 males). The mean age of the patients with pSS was 58±12 years, and the mean duration of the disease was 9±4 years. The serum samples were obtained after informed consent and the study protocol was approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland.

The levels of the various anti-CA antibodies were not associated with keratoconjunctivitis sicca or labial salivary gland histological grades (data not shown). However, the median (interquartile range) relative absorbance values for serum anti-CA I (1.30 (1.18-1.52) vs. 1.25 (1.10-1.33), p=0.036) and anti-CA VII (1.25 (1.16-1.36) vs. 1.17 (1.09-1.28), p=0.022) antibody levels were higher (Mann-Whitney U-test) in pSS patients suffering from persistent dry cough (n=34) compared with other patients (n=40), respectively. No associations were found with pulmonary fibrosis as judged from plain chest x-ray (data not shown). However, in a recent study, anti-CA I antibodies in patients with various connective tissue diseases were found to be associated with interstitial lung disease when studied with a more sensitive method, i.e. HRCT (6).

The levels of anti-CA I antibodies (1.30 (1.19-1.51) vs. 1.23 (1.11-1.33), p=0.041) tended also to be higher in pSS patients with dental prostheses (n=39) compared with those with their own teeth (n=35), respectively. A solid interpretation of this finding would need comparisons of antibody levels before and after receiving the prosthesis. Interestingly, CA VI is probably an important factor contributing to cariogenic processes by unknown mechanisms (7), and the function of other CA isoenzymes is also essential in saliva production (8).

The presence of anti-CA antibodies can naturally be related to a broad autoimmune response against a large variety of self molecules in pSS patients, and, indeed, the majority of anti-CA antibodies correlated with circulating autoantibodies (Table 1). However, anti-CA VII and anti-CA XIII antibodies also correlated with the concentration of serum beta-2 microglobulin, which has been associated e.g. with the development of pSS among subjects with sicca symptoms (9) and with pulmonary findings in pSS (10).

Our results suggest that antibodies to CA I and CA VII might be associated with such troublesome consequences of mucosal dryness as persistent dry cough as a sicca symptom of the respiratory tract in pSS patients, and anti-CA I antibodies also with dental decay. Further studies are needed to confirm these findings.

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Table I. Correlation (r) of serum anti-carbonic anhydrase antibody levels (anti-CA I, II, VI, VII, XIII) with demographic and immunological findings in 74 patients with primary Sjögren’s syndrome (Spearman correlation coefficient)

<table>
<thead>
<tr>
<th>Variable</th>
<th>r for CA I</th>
<th>p-value</th>
<th>r for CA II</th>
<th>p-value</th>
<th>r for CA VI</th>
<th>p-value</th>
<th>r for CA VII</th>
<th>p-value</th>
<th>r for CA XIII</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.136</td>
<td>0.136</td>
<td>-0.005</td>
<td>0.882</td>
<td>-0.176</td>
<td>0.134</td>
<td>0.183</td>
<td>0.119</td>
<td>0.183</td>
<td>0.119</td>
</tr>
<tr>
<td>Disease duration</td>
<td>-0.050</td>
<td>0.671</td>
<td>0.058</td>
<td>0.623</td>
<td>0.054</td>
<td>0.646</td>
<td>-0.035</td>
<td>0.764</td>
<td>0.018</td>
<td>0.879</td>
</tr>
<tr>
<td>ESR</td>
<td>0.248</td>
<td>0.033</td>
<td>0.297</td>
<td>&lt;0.0001</td>
<td>0.543</td>
<td>&lt;0.0001</td>
<td>0.441</td>
<td>&lt;0.0001</td>
<td>0.550</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP</td>
<td>0.188</td>
<td>0.112</td>
<td>-0.072</td>
<td>0.544</td>
<td>0.047</td>
<td>0.695</td>
<td>0.231</td>
<td>0.049</td>
<td>0.085</td>
<td>0.475</td>
</tr>
<tr>
<td>Serum protein</td>
<td>0.324</td>
<td>0.005</td>
<td>0.426</td>
<td>&lt;0.0001</td>
<td>0.543</td>
<td>&lt;0.0001</td>
<td>0.420</td>
<td>&lt;0.0001</td>
<td>0.553</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>0.221</td>
<td>0.071</td>
<td>0.455</td>
<td>&lt;0.0001</td>
<td>0.555</td>
<td>&lt;0.0001</td>
<td>0.285</td>
<td>0.014</td>
<td>0.514</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum IgA</td>
<td>0.021</td>
<td>0.862</td>
<td>0.086</td>
<td>0.465</td>
<td>0.194</td>
<td>0.098</td>
<td>0.076</td>
<td>0.520</td>
<td>0.118</td>
<td>0.318</td>
</tr>
<tr>
<td>Serum IgM</td>
<td>0.235</td>
<td>0.044</td>
<td>0.057</td>
<td>0.629</td>
<td>0.075</td>
<td>0.528</td>
<td>0.238</td>
<td>0.041</td>
<td>0.080</td>
<td>0.498</td>
</tr>
<tr>
<td>Serum beta-2 microglobulin</td>
<td>0.204</td>
<td>0.082</td>
<td>0.192</td>
<td>0.102</td>
<td>0.209</td>
<td>0.074</td>
<td>0.275</td>
<td>0.018</td>
<td>0.278</td>
<td>0.016</td>
</tr>
<tr>
<td>RF</td>
<td>0.111</td>
<td>0.346</td>
<td>0.419</td>
<td>&lt;0.0001</td>
<td>0.404</td>
<td>&lt;0.0001</td>
<td>0.174</td>
<td>0.137</td>
<td>0.394</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ANA</td>
<td>0.032</td>
<td>0.787</td>
<td>0.310</td>
<td>0.007</td>
<td>0.336</td>
<td>0.003</td>
<td>0.145</td>
<td>0.218</td>
<td>0.291</td>
<td>0.012</td>
</tr>
<tr>
<td>anti-SSA antibodies</td>
<td>0.020</td>
<td>0.864</td>
<td>0.113</td>
<td>0.329</td>
<td>0.297</td>
<td>0.011</td>
<td>0.076</td>
<td>0.524</td>
<td>0.271</td>
<td>0.020</td>
</tr>
<tr>
<td>anti-SSB antibodies</td>
<td>0.088</td>
<td>0.457</td>
<td>0.095</td>
<td>0.424</td>
<td>0.230</td>
<td>0.050</td>
<td>0.230</td>
<td>0.050</td>
<td>0.202</td>
<td>0.087</td>
</tr>
</tbody>
</table>

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ANA: anti-nuclear antibodies.
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References
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