Selective Increase of IgA Rheumatoid Factor in Patients with Gluten Sensitivity

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An increased prevalence of raised autoantibodies, including rheumatoid factor, has been reported in patients with gluten sensitivity. However, rheumatoid factor has only been measured in small groups of patients and the findings have been conflicting. In this study IgM, IgG and IgA rheumatoid factor was measured in 89 patients with dermatitis herpetiformis and 22 patients with coeliac disease and compared with 89 normal controls. There was an increased prevalence of elevated IgA rheumatoid factor in the patients with dermatitis herpetiformis (13.5%; p = 0.036) and coeliac disease (18.2%; p = 0.078), while no such increase was found for the IgM or IgG rheumatoid factor isotypes. This selective increase of IgA rheumatoid factor suggests that rheumatoid factor production in patients with gluten sensitivity primarily results from immunological activation in the gut mucosa. Key words: dermatitis herpetiformis; coeliac disease; autoantibodies.

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IgA antibodies may be of pathogenic significance in dermatitis herpetiformis (DH) but probably not in coeliac disease (CD). IgA-containing circulating immune complexes have been reported both in DH and CD patients (1), but deposits of IgA antibodies are only found in the papillary dermis of uninvolved skin in DH but not in CD patients (2). It has not been possible to elute functional IgA antibodies from DH skin and their specificity is therefore not known. However, the IgA deposits gradually disappear in patients on gluten-free diet, suggesting that the IgA in the skin of DH patients originates from an immune response to components of gluten in the gut (3). Raised levels of various autoantibodies have also been reported both in DH and CD patients, including antibodies against thyroid antigens (4–7), endomysium (8), reticulin (8), parietal cells (4, 9), nuclear antigens (9) and IgG rheumatoid factor, RF (10–12). In contrast, DH patients have been found to have lower levels of IgA antibodies to high molecular weight glutenin and human elastin than both normal controls and CD patients (13). The reduction of IgA elastin antibodies was more pronounced in patients on gluten-free diet, and it was therefore proposed that glutenin antibodies which cross-react with human elastin may accumulate in the skin of DH patients and thereby be depleted from the circulating pool (13). However, analysis of autoantibody isotypes has generally not been made in patients with gluten sensitivity, and it is therefore not known whether low levels of autoantibodies of the IgA isotype constitute a general phenomenon in DH. In this paper we report a preferential increase of IgA RF in patients with DH and CD.

MATERIALS AND METHODS

Patients and samples

Altogether 200 samples of serum were measured for IgM, IgG, and IgA RF. Of these 63 were from DH patients on a gluten-free diet, 26 from DH patients on a normal diet and 22 from CD patients. DH patients were considered to adhere strictly to gluten-free diet if they were symptom free without dapsone treatment and their gliadin antibodies were not raised. Samples from 89 randomly selected healthy adults, aged 31–50 years, were used as controls. The DH and control samples had all previously been measured for IgG and IgA antibodies against gliadin, high molecular weight glutenin, human aortic elastin (13) and also for antibodies to various food antigens (manuscript in preparation).

Measurement of RF

RF isotypes were measured by a modified ELISA system, which has been described in detail elsewhere (14). Briefly, Dynatech Immunolone plates were coated over night at 4°C with a 40 µg/ml solution of purified rabbit IgG (Sigma). Dilutions of the serum samples were incubated for 3 h at room temperature. The IgG and IgM RF isotypes were detected with alkaline phosphatase (AP)-coupled mouse monoclonal anti-human IgM (Sigma, clone MB-11) and anti-human IgG (Sigma, clone GG-5) antibodies. IgA RF was detected with a mouse monoclonal anti-human IgA antibody (Oxoid, clone 2D7 M26) incubated at 4°C over night, followed by AP-coupled, rabbit anti-mouse antibody (DakoPas). All AP-coupled detector antibodies were incubated for 2 h at room temperature. Finally a 10 mg/ml p-nitrophenyl phosphate substrate solution was added and the absorbance read at 405 nm in a Titertek Multiscan (Flow Laboratories) when absorbance of the strongest standard dilution had reached 1.5–1.8. Results were expressed in arbitrary units (AU/ml) according to serial dilutions of a local standard prepared from sera collected from 11 patients with rheumatoid arthritis (RA) and high levels of all RF isotypes. The upper limit of normal for the RF isotypes was set at the 95% cutoff level for the control group. The interassay variability was found to be 16% and the intraassay variability 14%. The detection limit was 10 AU/ml for IgM RF, 6 AU/ml for IgG RF and 6 AU/ml for IgA RF. In this ELISA assay system approximately 90% of RA patients have elevated levels of one or more RF isotypes (IgM RF in 70%, IgG RF in 45% and IgA RF in 60% of RA patients).

Statistical analysis

For evaluation of the results the chi-square test (with Yates correction for expected frequencies less than five), the Mann-Whitney U-test and Spearman rank correlation coefficient were used. The level of significance was set at p < 0.05.

RESULTS

Of the DH patients 12 (13.5%) had elevated levels of IgA RF (Fig. 1, p = 0.036). No difference in IgA RF levels was observed between DH patients on gluten-free diet and DH patients on normal diet (Fig. 2, p = 0.181). Patients with CD also tended to have raised levels of IgA RF (18.2%; p = 0.078). In contrast, no increase was found in IgM RF and IgG RF in the DH or CD patients.

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As shown in Table I, the DH patients had significantly lower levels of IgA antibodies to both elastin and glutenin than both the controls and the CD patients. No difference was found in IgA antibodies to glutenin or elastin between the IgA RF positive and negative DH patients (Table I). Patients with low levels of IgA antibodies against glutenin and elastin did not have lower IgA RF, and the IgA RF was not reduced in patients on gluten-free diet (data not shown).

When all detectable RF levels were analysed, a significant positive correlation was found between IgM and IgA RF and between IgG and IgA RF, but not between IgM and IgG RF, both in the controls and the patients.

Table I. Comparison of IgA antibody levels (median) to elastin and glutenin in controls, CD patients and DH patients with elevated and normal levels of IgA RF

<table>
<thead>
<tr>
<th>IgA antibodies to:</th>
<th>Elastin</th>
<th>Glutenin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DH patients with elevated IgA RF (n=12)</td>
<td>17.0*</td>
<td>17.8</td>
</tr>
<tr>
<td>DH patients with normal IgA RF (n=77)</td>
<td>21.0</td>
<td>14.8</td>
</tr>
<tr>
<td>CD patients (n=22)</td>
<td>45.0* *</td>
<td>30.8*</td>
</tr>
<tr>
<td>Controls (n=89)</td>
<td>30.0* *</td>
<td>21.0*</td>
</tr>
</tbody>
</table>

* Median antibody level (AU/ml) in each group. Significance as compared with all the 89 DH patients: *p<0.05  **p<0.0001.

DISCUSSION

In this paper we report a selective increase in the prevalence of raised IgA RF in patients with gluten sensitivity. It has previously been claimed that IgM RF, IgG RF and IgA RF are all elevated in DH patients (10), while others have only reported elevation of IgM RF (11). To our knowledge no information is available about the RF isotopes in patients with CD. In agreement with the finding that IgA RF can persist for many years in symptom-free individuals (15, 16), DH patients on gluten-free diet did not have lower IgA RF than patients on normal diet. This contrasts with the observation that IgA antibodies to human elastin are reduced in DH patients, particularly those on gluten free diet (13) and supports the notion that IgA elastin antibodies may be selectively taken up by microvillar elastin components in the skin of DH patients (17).

The observation that a correlation exists between IgM RF and IgA RF and between IgG RF and IgA RF, but not between IgM RF and IgG RF, is in agreement with previous findings for patients with rheumatic disorders (16).

It has been reported that patients with Sjögren’s syndrome and other symptoms originating from mucous membranes tend to have isolated or preferential increase in IgA RF (18, 19). Our finding of an increased prevalence of raised IgA RF, but not IgM RF or IgG RF, in patients with gluten sensitivity is therefore likely to reflect an increased immunological activity in the gut mucosa.

Increased incidence of intestinal lymphoma has been noted in patients with CD (20, 21) and also in DH (22, 23), although strict adherence to gluten-free diet may reduce the risk of developing malignancy (23–25). We have previously shown that elevated levels of IgA RF in non-rheumatic individuals, but not other RF isotopes, are associated with increased incidence of cancer (15). Thus, elevation of IgA RF in patients with gluten sensitivity may reflect an excessive stimulation or activity of the immune system at mucosal level, which may eventually lead to malignancy.

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