IgA-α₁ antitrypsin complexes in ankylosing spondylitis

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SUMMARY A study of 95 serum samples from 61 patients with ankylosing spondylitis (AS) showed that 21 patients (34%) had raised levels of IgA-α₁ antitrypsin complexes. These were associated with active disease as measured by a clinical index and also with erythrocyte sedimentation rate, C reactive protein, and serum IgA. In particular, an association was noted between ‘extraspinal’ manifestations of AS such as synovitis, uveitis, and active inflammatory properties of these complexes. It is suggested that these complexes may have a role in the pathogenesis of such clinical manifestations.

Ankylosing spondylitis (AS) is considered to be an inflammatory disease, though the underlying mechanisms and predisposing factors remain an area of intense debate. Clinically and pathologically two different types of inflammation may be recognised; firstly, enthesitis—inflammation of the attachment of ligaments and tendons to bone and, secondly, synovitis, similar to that found in other inflammatory arthropathies.

Serological parameters, such as acute phase proteins and erythrocyte sedimentation rate (ESR), seem often to be poor guides to the underlying disease process in AS, correlating poorly with clinical symptoms. One of the most commonly reported abnormalities has been the presence of raised concentrations of serum IgA, which, it has been speculated, is an expression of underlying pathogenetic mechanisms that are possibly gut related. Likewise, in rheumatoid arthritis (RA) evidence suggests that the abnormally raised serum IgA concentrations which are frequently observed may be directly related to pathogenesis as induction of selective IgA deficiency by treatment of such patients with second line drugs is often associated with disease remission. Moreover, this would result in lack of formation of the covalently linked complex between IgA and the major antiprotease α₁ antitrypsin, which has been shown to possess potentially harmful biological properties.

Patients and methods

Patients Ninety five serum samples were obtained from 61 patients (52 male, nine female) attending the spondylitis clinic at Selly Oak Hospital, Birmingham. Their average age was 41 years (range 21–70). Fifty six (48 male, eight female) had definite AS and five possible AS (American Rheumatism Association criteria, New York 1966). Table 1 gives further clinical details.

All patients were assessed clinically and divided into four groups on the basis of their symptoms at the time the samples were taken: inactive, mild, moderate or severe. The latter group comprised 23 patients with disease duration greater than 17 years. Nineteen patients (11 male, eight female) had established disease and were therefore included in the severe group.

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Table 1 Clinical details of patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>M/F</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>Psoriasis</th>
<th>IBD*</th>
<th>ESD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite AS (n=56)</td>
<td>48/8</td>
<td>41</td>
<td>17</td>
<td>5</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Possible AS (n=5)</td>
<td>4/1</td>
<td>28</td>
<td>7.5</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>

*IBD=inflammatory bowel disease; ESD=extraspinal disease—for example, synovitis and uveitis.
moderate, and severe disease. All patients with active inflammation such as synovitis, colitis or acute uveitis were included in the severe group. Routine measurements of ESR, C reactive protein (CRP), and IgA were performed as part of the assessment in the research clinic.

**CONTROLS**

Serum samples from 21 normal individuals (laboratory staff) and 38 patients with RA were included as negative and positive controls.

**METHODS**

Serum samples were stored frozen at -20°C until analysis. IgA-α₁ antitrypsin complexes were estimated by crossed immunoelectrophoresis using 1-25% anti-α₁ antitrypsin in the gel. The area under the slower moving peak, determined by planimetry, was taken as a measure in arbitrary units of the amount of the IgA-α₁ antitrypsin complex present.

**Results**

Twenty one (34%) of the 61 patients with AS were found to have raised serum levels of the IgA-α₁ antitrypsin complex, but when the group as a whole was compared with the negative control group there was no significant difference between the means. This contrasts with the higher levels of the complex found in patients of the RA positive control group (Fig. 1). The circulating levels of complex correlated well, however, with IgA and CRP but showed less convincing correlations with ESR and clinical assessment (Figs 2-5).

Eleven serum samples (from 10 patients) were found to have levels of the complex that were raised by more than three standard deviations from the mean. Ten of these came from patients who had signs of active extraspinal inflammation such as synovitis, uveitis, and ulcerative colitis (Fig. 6).
Significantly raised serum levels of antitrypsin complexes in patients with ankylosing spondylitis (AS) have been reported. Unlike in rheumatoid arthritis (RA), however, the mean serum level of the group as a whole was not significantly raised when compared with that of a group of normal individuals. Yet, if one studies the relation of this parameter with active spondylitis, as defined by both clinical and laboratory criteria, there is a significant association between the level of such circulating complexes and active disease. In particular, as the presence of synovitis, anterior uveitis, and active colitis was included in the definition of very active disease before the study, and as the highest levels (greater than 3SD from the mean) were in all but one case associated with extraspinal inflammation, the presence of high circulating levels of the IgA-α1 antitrypsin complex seems to be associated with this secondary inflammation in AS.

The presence of high concentrations of circulating IgA in both AS and RA has been considered to be an expression of underlying disease activity, rather than contributing directly to the pathogenetic process. Yet recent evidence in patients with RA suggests that IgA and in particular IgA-α1 antitrypsin complexes may have a much more active role. Clinically, the induction of disease remission in RA by second line agents has been associated with a selective IgA deficiency and has been described in patients treated with gold, d-penicillamine, sulphasalazine, and fenclofenac. Levels of the complex are high in active RA and fall when disease remission is induced with gold and penicillamine. In addition, very high levels of the complex are found in the synovial fluid in RA, whereas free IgA and α1 antitrypsin concentrations are higher in serum, implying that the complexes are formed...
within the joint. This has important pathological implications as recent in vitro studies have shown the complex to possess pro-inflammatory properties. Evidence suggests that apart from consuming large amounts of a major antiprotease (α₁ antitrypsin) the complexes themselves may elicit release of lysosomal enzymes from macrophages by a process dependent upon activation of the alternative complement pathway. High circulating concentrations of IgA seem to be a prerequisite for the formation of these complexes, whose levels are also markedly raised in the sera of patients with IgA myelomatosis.

Interestingly, a rapid rise in circulating IgA concentrations is found when arthritis is induced experimentally in rabbits by the intra-articular injection of antigen—for example, ovalbumin or altered autologous IgG—into animals presensitised by subcutaneous injection of the same antigen in Freund’s complete adjuvant. The possibility that IgA-α₁ antitrypsin complexes may contribute to this experimental arthritis is highlighted by the recent observation that the injection of the complex into the joints of unsensitised animals can result in a rapidly progressive and destructive arthritis (D R Stanworth and I V Lewin, unpublished observations).

In AS the primary lesion seems to be a non-specific inflammation of the enthesis—the site of attachment of ligaments and tendons to bone. Synovitis also occurs and both have been considered to be similar manifestations of the same disease. Unlike in RA, however, laboratory measures of inflammation in AS appear poor indicators of clinical disease activity, especially when the disease is predominantly spinal. Peripheral synovitis, however, does seem to be reflected by laboratory tests such as ESR and CRP. Raised serum IgA is also one of the most commonly reported abnormalities in AS, and as such has given rise to speculation about the role of the gastrointestinal tract and its immune system in the pathogenesis of the disease. Therefore, in view of the findings in RA and myeloma it is perhaps not surprising that this study has shown that circulating levels of IgA-α₁ antitrypsin complexes are raised in AS. The clear association between the levels of the complex, clinical evidence of extraspinal disease such as synovitis, uveitis, and colitis, and laboratory tests like ESR and CRP, suggests that the complex may have a much more active role in the pathogenesis of AS. This is particularly relevant when the data from the laboratory and animals studies are considered, suggesting that the complex forms when IgA concentrations rise and that in doing so may have a major role in the development of synovitis and other secondary inflammatory manifestations in AS.

Further studies are obviously needed to look at the levels of the complex in the sera and synovial fluid of patients with AS, and also to investigate its possible role in inflammatory bowel disease. It may be that in this condition, as in AS, IgA-α₁ antitrypsin complexes are contributing significantly to the disease process, especially to synovial inflammation.

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