Correlation of immunoglobulin and C reactive protein levels in ankylosing spondylitis and rheumatoid arthritis

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SUMMARY Serum C reactive protein (CRP), IgG, and IgA levels were measured in 22 patients with ankylosing spondylitis (AS) and in 20 patients with rheumatoid arthritis (RA) to study the regulation of these proteins in inflammatory disease states. In both RA and AS the mean CRP, IgG, and IgA levels were raised above normal values. Although IgA and CRP levels showed a significant positive correlation in RA ($r=0.53$, $p=0.02$), there was no correlation between these values in AS ($r=0.24$, $p=0.29$). The difference in correlation coefficients between the AS and RA groups was significant at a $p=0.05$ level. In RA the raised IgA levels may be another manifestation of the acute phase response, as shown by the good correlation between IgA and CRP in that disease. In AS, however, the IgA levels, although raised, do not correlate with CRP levels, suggesting that the mechanism of increase of IgA in the two diseases is different. Gut mediated immune stimulation has been proposed as a cause of raised IgA levels in AS.

Key words: mucosal immunity, acute phase reactants, humoral immunity, spondylarthropathy.

Laboratory markers of inflammation are considered useful in monitoring the disease activity and response to treatment of many rheumatic diseases. The erythrocyte sedimentation rate (ESR) is one such marker and has been shown to correlate with disease activity in RA and systemic lupus erythematosus.^{1,2} Acute phase proteins such as CRP have been shown to respond more quickly to changes in disease activity and may be more useful than the ESR.^{3,4} Immunoglobulin levels are also affected in RA. Most authors report raised serum IgG and IgA levels but only rarely increases in IgM levels.^{5,6} Since RA is a disease associated with polyclonal B cell activation,⁷ we would expect IgA levels to be raised in proportion to other immunoglobulins as well as the acute phase reactants.

In AS the importance of laboratory parameters is less clear. The ESR is notoriously unreliable as an

indicator of disease activity in AS.⁸ CRP levels have been found to correlate with the activity of the peripheral arthritis and not the spondylitis in AS.⁹⁻¹¹ A recent study, however, has shown that CRP levels as assessed quantitatively by nephelometry were extremely sensitive indicators of overall disease activity in AS.¹² Raised levels of IgG, IgA, and IgM also occur in AS but probably do not correlate with disease activity.^{13,14} Rarely, IgA deficiency has been seen in both AS¹⁵ and RA.¹⁶ To our knowledge only one group of researchers has shown that IgA levels are specifically raised in AS and correlate with disease activity.¹⁷ This finding is of interest because of speculation that AS is a reactive arthritis, triggered by a gastrointestinal antigen of possible microbial origin. Serum IgA levels may reflect this gastrointestinal immune stimulation and would therefore be raised out of proportion to other acute phase reactants. We undertook this study to clarify further the relation between immunoglobulin and CRP levels in RA and AS and to determine if IgA levels are regulated differently in the two diseases.

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Patients and methods

All patients who participated in this study were followed up in the Veterans Administration rheumatology clinics. Letters were sent to 59 patients known to have a seronegative spondylarthropathy. Twenty two patients with AS ultimately gave blood samples. All 22 patients were male, age range 35–70, mean age 53.1 years. The diagnosis of AS was made by clinical criteria with confirmation by spine and sacroiliac joint *x* rays. Eleven patients were known to be HLA-B27 positive, four were negative, and seven were of unknown HLA type. All were being treated with non-steroidal anti-inflammatory drugs or pain killers, or both. For comparison we also obtained blood samples from 20 patients with classical or definite seropositive RA (age range 46–71, mean age 63.1 years). These patients were all being treated with remittive agents and non-steroidal anti-inflammatory drugs, and were selected randomly from our clinic system.

Sera were stored at –20°C, and all samples were run as a group without knowledge of the patients' diagnoses. IgG and IgA levels were measured by radial immunodiffusion with commercially available protein standards.¹⁸ CRP levels were measured by rate nephelometry.¹⁹

Results

Serum immunoglobulin and CRP determinations are shown in Table 1. As compared with normal historical controls, moderately raised mean IgA and IgG levels were found in both patient groups. No significant difference was found between the patients

with RA or AS. Mean CRP levels were also found to be raised, but the values were spread over a large range.

The data were analysed by univariate analysis and were not normally distributed by Shapiro-Wilk's statistic. Non-parametric testing with Spearman's correlation coefficient was used to analyse the data further. The data are plotted in Figs 1 and 2. IgA was found to correlate significantly with CRP levels only in RA (*r*=0.53, *p*=0.02). In AS there was no correlation between IgA and CRP (*r*=0.24, *p*=0.29). These correlation coefficients were transformed and then compared with a normal distribution.

Fig. 1 Correlation of CRP and IgA levels in rheumatoid arthritis. Results from 20 patients are shown. Correlation is significant at *p*=0.02 (*r*=0.53) by Spearman's correlation coefficient. (mg/dl×10=g/l).

Fig. 2 Correlation of CRP and IgA levels in ankylosing spondylitis. Results from 22 patients are shown. Correlation between IgA and CRP is not significant (*p*=0.29) by Spearman's correlation coefficient.

Table 1 Results of IgG, IgA, and CRP levels in AS and RA*

	RA	AS	Normal values
IgG (mg/dl)			
Mean (SEM)	1480 (124)	1350 (86)	1250+
Range	742–2640	796–2510	650–1600
IgA (mg/dl)			
Mean (SEM)	278 (37)	294 (31)	210+
Range	69–729	103–686	100–400
CRP (mg/dl)			
Mean (SEM)	1.96 (0.47)	2.01 (0.41)	0.8‡
Range	<0.6–8.04	<0.6–7.96	≤2.0

*Immunoglobulin levels were measured by radial immunodiffusion with commercially obtained protein standards. CRP determinations were made by rate nephelometry.

†See reference 20.

‡See reference 21.

Conversion: mg/dl×10=mg/l.

tion by Z testing.²² By this method IgA-CRP correlations in RA and AS were found to be significantly different at $p=0.05$.

Discussion

Many inflammatory rheumatic diseases cause increases in the erythrocyte sedimentation rate, acute phase protein levels, and immunoglobulin levels and cause haematological changes such as leucocytosis and thrombocytosis. These markers of inflammation, though not useful diagnostically, have been found to be helpful in monitoring disease activity and in following up the response to treatment. In RA, raised ESR and CRP levels are commonly found and may predict erosive disease.¹ Non-steroidal anti-inflammatory drugs do not alter these levels, but gold salts and other remittive treatments have been shown to return these levels to normal.²³ In AS, raised ESR and CRP levels are variable, and reports regarding their correlation with activity of disease are conflicting.¹⁰ Recently, however, a report has suggested that CRP levels measured by rate nephelometry, as was used in this study, correlate well with overall disease activity in AS.¹²

We studied sera from 42 patients with RA and AS for both CRP and immunoglobulin levels, looking for a relation between these variables in different disease states. Presumably, an inflammatory stimulus in a joint or enthesis would cause increases in both levels, and a positive correlation would be seen in both AS and RA, but a markedly different relationship was found.

In RA we found moderate increases of IgG, IgA, and CRP levels as compared with normal historical controls, and as other authors have found.¹⁻⁶ When paired sets of data from each patient with RA were plotted (Fig. 1) a significant correlation was seen between IgA and CRP levels ($r=0.53$, $p=0.02$ by Spearman's correlation coefficient). The increase of IgA levels in these patients may be a result of the same inflammatory stimulus that causes an increase in the CRP level. In addition, polyclonal B cell activation is known to accompany RA, and may account for the increases in both IgA and IgG levels.⁷

In AS, raised IgG, IgA, and CRP levels were found that did not differ significantly from those in RA. Other authors have also reported these increases.^{9 10 13 14 17} No correlation was found, however, between CRP and IgA in AS ($r=0.24$, $p=0.29$). Fig. 2 shows the wide scatter of these data points.

Therefore, we have shown that IgA levels, though raised in AS, do not correlate with CRP levels as they do in RA, possibly owing to a specific stimulus

to IgA production in AS unrelated to the stimulation of acute phase reactants. One other study has reported that the ESR and serum IgA levels do not correlate with each other and suggested that both parameters reflect different aspects of disease.²⁴ An important source of serum IgA is the gut associated lymphoid tissue, and increased serum IgA levels may reflect gastrointestinal immune stimulation.²⁵ Ingested antigens or those derived from bacteria residing in the gut may be transported across the mucosa and contact gut associated lymphoid tissue lymphocytes, initiating an immune process. Isolation of klebsiella and enterobacter species from the faeces of patients with AS has been shown to correlate with increased CRP and ESR, but IgA measurements were not made in that study.²⁶ Faecal klebsiella species have also been correlated with increased activity of disease in AS.^{27 28} Patients with AS have raised *Klebsiella pneumoniae* specific serum IgA levels,²⁹ and these antibodies may account for some of the IgA increase. Raised IgA levels have also been found in Reiter's disease,³⁰ a disease with a more clearly reactive component.³¹ It is possible that abnormal bowel permeability in AS may be a factor leading to increased absorption of gut antigens and subsequent immune complex associated arthritis.^{32 33} Raised serum IgA levels in patients with AS may therefore be a marker of the pathogenesis of this disease.

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