Serum immunoglobulins in acute anterior uveitis

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SUMMARY   Serum levels of immunoglobulin A, G, and M were examined in 99 patients with acute anterior uveitis (AAU). The mean level of serum IgA was raised ($p < 0.001$) in AAU patients when compared with healthy control subjects. The levels of serum IgG and IgM were not significantly different from those in the control group. The raised levels of serum IgA were found to occur predominantly in the HLA-B27 positive group of patients ($p < 0.001$) and were highest in HLA-B27 positive patients with sacroiliitis or associated spondylarthritic diseases ($p < 0.001$). The HLA-B27 negative group of AAU patients did not have a significantly raised mean serum IgA. The raised level of serum IgA in HLA-B27 positive AAU patients suggests that there has been a response to an environmental or infectious agent(s) acting across a mucosal tissue in these patients. This agent could be responsible for the initiation of the acute ocular inflammation.

The aetiology of acute anterior uveitis (AAU) is not known. It is probably a collection of heterogeneous conditions. Ankylosing spondylitis (AS) and other related forms of arthritis known collectively as the seronegative spondylarthropathies (SpA) are known to be associated with AAU.[1] These associations became clearer following the discovery that over 90% of AS patients and a high proportion of patients with SpA carried the HLA tissue antigen B27.[2] Subsequent studies showed that about 50% of all AAU patients possessed the B27 antigen, and that virtually all AAU patients with an associated arthritis were found in the B27 positive (B27+) group.[3][4]

Other studies have shown that AS patients with active inflammatory disease had raised serum and salivary secretory IgA, whereas AS patients with inactive disease had normal values.[5][6] It was suggested that these results reflected an immunological response to an infectious agent acting upon a mucosal surface in these patients.

A common aetiology and pathogenesis for the eye inflammation in HLA-B27 positive AAU and the spinal and peripheral joint inflammation of AS has been proposed.[7] It was therefore decided to examine serum immunoglobulin levels in AAU patients and to determine if there were differences between the HLA B27+ and B27− subgroups.

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Patients and methods

A uveitis research clinic has been established at the Royal Victorian Eye and Ear Hospital. The first 100 consecutive patients presenting within four weeks of an onset of an acute first attack or a recurrence of AAU were included in the study. Patients with chronic uveitis (that is, requiring more than three months' treatment) or with posterior uveitis were excluded. The mean age of the patients was 41·5 years with a range of 13 to 78 years, and 54 were male. Sixtysix healthy non-hospital subjects recruited from general practitioner lists and university staff provided the control group. The mean age of the control subjects was 36·3 years with a range of 16 to 78 years, and 34 were males. Each patient and control subject was examined, a history obtained, and blood drawn for examination. Where indicated pelvic or spinal radiographs were taken. Tissue typing was performed by the standard microlymphocytotoxicity tests. Serum immunoglobulins were measured by radial immunodiffusion using commercially available plates (Calbiochem-Behring). Statistical analyses were performed by Student's *t* test.

Results

One patient was excluded as his blood sample was subsequently discovered to have been taken six weeks after the onset of his ocular symptoms. Of the remain-

Table 1 *Serum immunoglobulins in patients with acute anterior uveitis in mg/l*

		IgA±(SEM)	IgG±(SEM)	IgM (SEM)
Patients	HLA−B27− SpA− n=46	231·5±16·6	1137±52	135·6±8·3
	HLA−B27− SpA+ n=5	292·2±89·2	918±81	139·4±22·0
	HLA−B27+ SpA− n=23	257·8±15·8	1114±72	140·6±13·8
	HLA−B27+ SpA+ n=25	296·8±22·3	1284±63	156·3±17·8
Controls	n=66	195·4±11·05	1219±40	149·8±8·1

ing 99 patients 48 (48%) were found to be B27+. Thirty patients were found to have an associated rheumatic disease. Of those 25 were B27+ and either had AS or typical back pain symptoms plus radiological sacroiliitis. There were five patients who were B27− with associated rheumatic diseases. One of these patients had Behçet's disease and carried the appropriate tissue marker HLA-B5.1. Two other patients had psoriasis and peripheral arthritis. None of these three had sacroiliitis. Because of the heterogeneous rheumatic conditions and the small numbers of patients in this group their results were excluded from the main statistical analysis and analysed separately. The results of the mean serum immunoglobulin and standard errors of the mean of the various patient and control groups are shown in Table 1.

There was no clinical evidence to suggest that patients with SpA had an exacerbation of arthritis during their episode of AAU.

Serum IgA. The mean serum IgA and standard errors of the mean in each patient group are shown in Fig. 1. There was a significant increase in mean serum IgA in all the AAU patient groups combined when compared with controls ($t=3·83$, $p<0·001$). This elevation was predominantly due to the HLA-B27+ patient groups ($t=4·29$, $p<0·001$) and particularly to the B27+ patients with SpA ($t=4·08$, $p<0·001$). There was no significant difference in mean IgA between controls and the B27− patient group ($t=1·81$, NS). There was a significant difference in mean serum IgA when the B27+ group was compared with the B27− group ($t=2·04$, $p<0·05$). There was no significant difference in IgA between the B27+ SpA+ and B27+ SpA− groups ($t=1·24$, NS).

Serum IgG. The results for mean levels of serum IgG are shown in Fig. 2. There were no significant
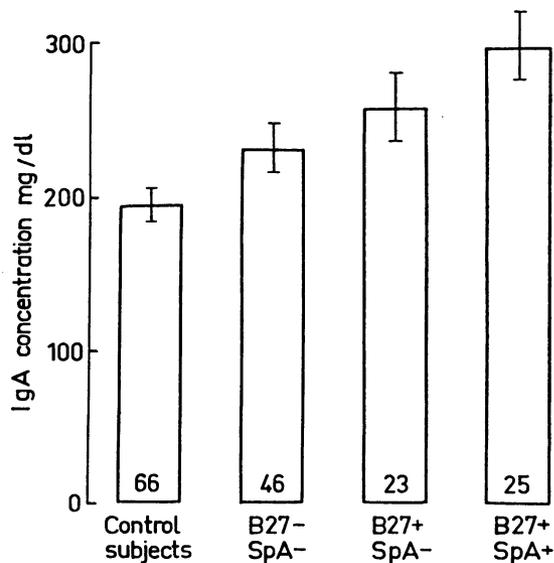

Fig. 1   *Mean serum IgA±SEM in control subjects, and in three groups of AAU patients: B27− SpA−, B27+ SpA−, B27+, SpA+.*
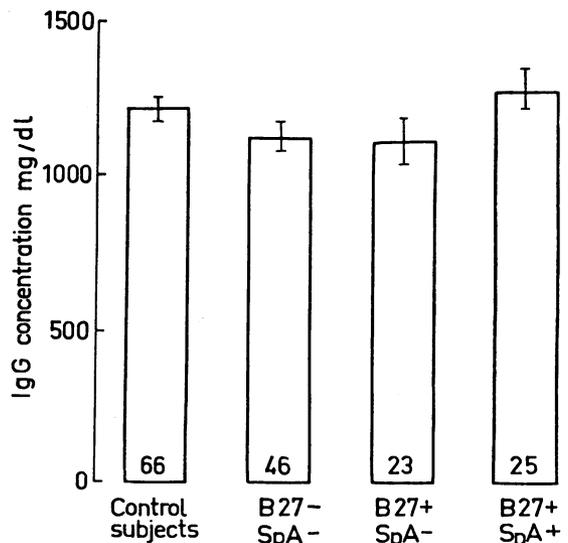

Fig. 2   *Mean serum IgG±SEM in control subjects and in three groups of AAU patients: B27− SpA−, B27+ SpA−, B27+, SpA+.*
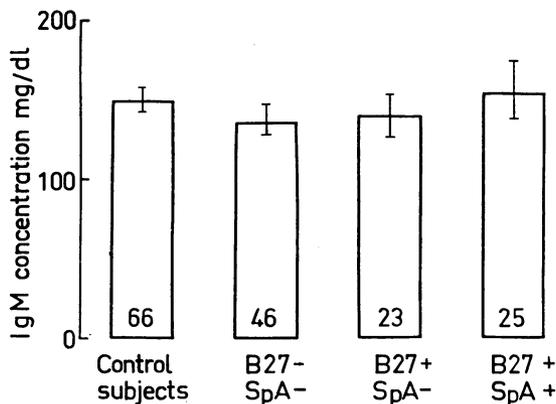
Fig. 3   *Mean serum IgM±SEM in control subjects and in three groups of AAU patients: B27− SpA−, B27+ SpA−, B27+, SpA+.*

differences in any of the patient groups studied when compared with control subjects. However, patients who were B27− SpA− had a significantly lower mean serum IgG than the B27+ SpA+ patient group ($t=2\cdot04$, $p<0\cdot05$).

Serum IgM. The results for serum IgM are shown in Fig. 3. There were no significant differences between the serum IgM values of any of the AAU patient subgroups and control subjects or between patient subgroups.

Discussion

The results show that in our series just under 50% of patients with AAU carry the B27 antigen. Thirty out of 99 patients were found to have an associated SpA. Of these patients 25 had the HLA B27+ antigen. These results are in close agreement with previous studies.[3][4] It is clear that most AAU patients who have an associated rheumatic disease carry the HLA-B27 antigen.

The results show a striking increase of mean serum IgA in B27+ AAU patients and particularly the B27+ SpA+ patients. The levels obtained were similar to those found in AS patients with clinically and bio-chemically active inflammatory disease and were higher than the levels found in AS patients with inactive inflammatory disease.[6]

The critical factor segregating the AAU patient groups into a high or a normal level of IgA appeared to be the presence of HLA-B27. The B27− patients as a group did not have a significantly raised IgA above controls, whereas the B27+ patients did. In addition, the serum IgA in B27+ patients with and without arthritis was not significantly different.

Statistical analysis of the immunoglobulin in the five B27− SpA+ patients was not carried out, as there was only a small number of values and a very wide scatter of results obtained.

It is of note that in all cases examined patients with an associated SpA did not have a clinically significant exacerbation of arthritis or sacroiliac symptoms during the episode of AAU. It is presumed that the raised serum IgA was related to the episode of AAU. However, low grade asymptomatic spinal inflam-mation (as demonstrated by increased radioisotope uptake) in the sacroiliac joints during AAU has been reported.[8] This question of low grade extraocular inflammation occuring during attacks of AAU needs to be assessed by further studies.

Previous investigations on immunoglobulin levels in AAU have been conflicting. Norn reported an increase in serum IgA and IgG but not IgM in patients with AAU.[9] These results were in marked contrast to those of Rahi *et al.*, who noted a rise of serum IgM but not IgG or IgA.[10] It should be noted that both of these studies were carried out prior to the availability of HLA tissue typing. Our findings are more in favour of those reported by Norn, but we did not demonstrate a raised serum IgG. If anything our studies suggest a mild decrease in serum IgG in the HLA-B27− patient group.

We have previously demonstrated that patients with active inflammatory disease in AS (nearly all of whom are B27+) had a raised serum IgA.[6] Com-parable results have been obtained by other investi-gators who also reported a rise in salivary secretory IgA.[6] Plasma cells in the mucosal associated lymphoid tissue (MALT) are the major source of IgA.[11] Investi-gations in animals raised in germ-free conditions have shown that after oral immunisation the main specific plasma cell response is IgA in character, and nearly all the circulating specific antibody is IgA.[12] It has been postulated that the findings of a raised serum IgA in active AS suggested that an infectious agent (probably acting across the gastrointestinal tract) is stimulating the production of serum IgA and that this micro-organism may also be responsible for the active inflammation. The finding of a raised serum IgA in B27+ AAU patients (but not in B27− patients) suggests that a similar process occurs during AAU in B27+ patients. Data in preparation suggests that a specific gram negative enteric micro-organism may be recovered from the faeces of a significant propor-tion of cases of AAU.

Examination of follow-up sera after the ocular in-flammation has settled may indicate whether raised serum IgA values in AAU return to the normal range. This may provide further evidence of a direct temporal relationship between episodes of AAU and raised serum IgA. Recent studies have reported that patients with AS had raised levels of IgA antibody to klebsiella micro-organisms.[13] It may be useful to

search for a specific antibody to Gram-negative intestinal bacteria in AAU.

Investigations during epidemics of dysentery have shown that infection with Gram-negative enteric pathogens such as shigella,[14] salmonella,[15] or *Yersinia enterocolitica*[16] are capable of initiating or triggering episodes of AAU. The individuals susceptible to this postdiarrhoeal AAU were frequently found to carry the HLA-B27 antigen and often developed other extraintestinal features such as arthritis at the same time. We have reported that *Klebsiella pneumoniae*, another Gram-negative micro-organism, is found more frequently in the faeces of AAU patients during acute exacerbations of inflammation of AS[17] and during episodes of AAU in AS.[18] These results have been confirmed by others.[19-21]

Our results showing a raised serum IgA in B27+ AAU patients suggest that a search for Gram-negative intestinal bacteria and raised Gram-negative bacterial antibody levels in AAU would be of value.

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