

Acute anterior uveitis and hepatitis B virus infection

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SUMMARY The aetiology of acute anterior uveitis (AAU) in the great majority of cases is unclear. Various infective agents have been postulated, however, as playing a direct or indirect part in the disease process, possibly via an immune-complex vasculitis. In an earlier study we concluded that, contrary to a previous report, hepatitis B virus (HBV) played only a small role, if any, in the pathogenesis of uveitis in Great Britain. Since we did not look for other markers of HBV infection other than hepatitis B surface antigen (HBsAg), it is possible that some cases of recent HBV infection may have been missed. In the present study 49 patients with AAU were tested for markers of hepatitis B infection. Sera from all patients tested were found to be negative for HBsAg and for antibody to the HBV core (anti-HBc), excluding HBV as a significant cause of AAU in this country. Since the quest for an infective agent in AAU may remain unproductive, future research on the aetiopathogenesis of AAU should include the study of tissue 'vulnerability' and the local and systemic immunoregulatory factors which modulate inflammatory responses.

Acute anterior uveitis (AAU) is a painful, ill-understood eye condition. Many infective agents have been postulated in its pathogenesis. They include chlamydia,¹ klebsiella,² and other bacteria and herpes simplex and varicella-zoster viruses.³

Infection with hepatitis B virus (HBV) has been implicated in the development of certain forms of glomerulonephritis⁴ and polyarteritis nodosa.⁵ These are thought to be due to the deposition in the vascular tree of circulating immune complexes comprising HBV antigenic components and their respective antibodies. It is conceivable, therefore, that HBV could cause an immune-complex vasculitis in the eye leading to uveitis.

Evidence for this comes from two previous studies. Firstly, a Swiss study⁶ showed that sera from 13% of patients with various types of uveitis were positive for hepatitis B surface antigen (HBsAg) and that 23% were positive for antibody to HBsAg (anti-HBs). This was taken to indicate previous HBV infection. Secondly, a random survey showed that 2% of patients with uveitis in Great Britain had HBsAg in their serum.⁷ This prevalence was 10 times higher than expected. No markers other than HBsAg were looked for.

It was decided, therefore, to investigate a group of

patients with AAU, not only to screen for HBsAg but also to test for a reliable marker of past HBV infection which also would identify patients with recent infection who were negative for HBsAg. Antibody to the HBV core (anti-HBc) was used to investigate the prevalence of past HBV infection, as this antibody probably persists for life.

Materials and methods

Forty-nine patients with acute anterior uveitis who presented to the Casualty Department, Moorfields Eye Hospital, City Road, within two weeks of the onset of symptoms were included in the study. Patients with only a few cells in the anterior vitreous were also included, but any more significant vitreous activity or evidence of posterior segment inflammation excluded them from the study.

Venous blood was collected at the first attendance of the patient. Blood was allowed to clot, and the serum was separated and stored at -20°C prior to use. Sera were tested for HBsAg and anti-HBc by solid-phase radioimmunoassay.⁸

Results

Of the 49 patients tested 33 were male and 16 female. In three patients the disease was bilateral and in the

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rest unilateral. Three patients had associated ankylosing spondylitis (New York criteria), and only four had suffered previous attacks of AAU. Their ages ranged from 19 to 69 years (mean 35 years). Forty-two were British Caucasian, 3 Asian, 3 West Indian, and 1 Chinese.

All sera tested were negative for HBsAg and anti-HBc.

Discussion

The role of immune complexes in inflammatory eye disease was first suspected by Levine and Ward.⁹ Char *et al.*² showed increased levels of immune complexes in chronic uveitis. In studies reported from our department^{11,12} low levels of C3 were observed in pars planitis, and raised levels of C1q binding immune complexes were found in recurrent anterior uveitis, Behçet's syndrome, and pars planitis with retinal vasculitis. A case of acute uveitis developing in the course of arthritis with systemic vasculitis due to immune-complex deposition has been reported,¹³ and Dernouchamps *et al.*¹⁴ have demonstrated immune complexes in the aqueous of patients with heterochromic cyclitis. Recently experimental evidence from rabbits showed that immune complexes could be demonstrated in the aqueous during times of clinically evident inflammation in immunogenic uveitis.¹⁵ It is possible, therefore, that HBV infection could itself be a trigger for an immune-complex-mediated AAU, since HBV has been linked previously to various systemic diseases such as glomerulonephritis⁴ and polyarteritis nodosa⁵ where an immune-complex vasculitis is central to the organ damage.

The usual sequel to infection with HBV is a mild, often clinically inapparent, acute hepatitis which has an incubation period of some three months. Most infections will resolve completely with clearance of viral antigens from the blood and their replacement by specific antibodies. During this time the patient may complain of urticaria and arthralgia, perhaps as a result of deposition of circulating immune complexes. These non-hepatic manifestations, if they occur in the acute infection, are generally short-lived.

A proportion of infections do not resolve, and the patient remains persistently infected with HBV and is termed a carrier. Early in the carrier state the patient's serum will contain an additional antigen, called the e antigen (HBeAg). At some later stage this is replaced by specific antibody (anti-HBe). At this time it is possible for HBeAg and anti-HBe to coexist in the serum. In addition a small proportion of carriers may also have HBsAg and its antibody (anti-HBs) co-existent in their serum. Thus, in carriers, these two antigen systems may be related to the possible

formation of circulatory immune complexes and extrahepatic disease. Grob and associates⁶ demonstrated anti-HBs in the serum of 23% of patients with uveitis. The seroconversion for anti-HBs in acute infections is variable, and the absence of this antibody cannot be taken to exclude recent HBV infection. Therefore, in order to exclude precisely previous infection, sera were tested for anti-HBc. Even though some of our patients came from areas in the world where there is a higher prevalence of carriers—for example, 10–20% in Asia—sera from all 49 patients tested were shown to be negative for HBsAg and anti-HBc, that is, none had previously been infected by HBV. Although we have not tested a larger number of blood samples, the evidence suggests that neither acute nor chronic HBV infection plays any part in the pathogenesis of AAU in this country.

As the aetiology of AAU is largely unknown, it was reasonable to search for a possible infective agent, especially as various micro-organisms have been implicated in its pathogenesis, particularly viruses³—for example, herpes simplex, varicella-zoster, and adenovirus. A number of Gram-negative bacteria have also been associated with AAU and the HLA-B27 histocompatibility antigen. Here the inflammatory reaction may develop either due to deposition of immune complex^{16,17} or through a type II hypersensitivity reaction, because certain ocular antigens seem to bind antibodies to Gram-negative organisms such as klebsiella.² Since IgA levels are raised in some patients with anterior uveitis,¹⁸ the possibility of associated gastrointestinal infection by Gram-negative organisms and eventual specific antibody production is a strong possibility.

A current theory¹⁹ suggests that the infectious agent binds to and/or alters the B27 antigen in such a way that an aberrant immune response results. Similarly it has been proposed that virus infection may induce aberrant expression of HLA-DR on target tissues, thus allowing them to activate T cells, leading to autodestruction.²⁰ Chlamydia has also been postulated as being involved in the induction of AAU, and a recent study indicates a significant relationship between the cell mediated immune response to chlamydia group antigen and the HLA-B27 positive subgroup of patients with AAU.¹

Since the various agents implicated in AAU are not uncommon pathogens, the susceptibility of the individual must play a crucial role. This may represent several underlying immunological defects in these patients. Already various abnormalities have been reported. Nussenblatt *et al.*^{21,22} have found increased suppressor T-lymphocyte numbers and activity in patients with active posterior uveitis. Byrom *et al.*²³ found a T lymphopenia in patients with HLA-B27 +ve and -ve AAU, as did Wakefield *et al.*²⁴ but only

in HLA-B27 +ve individuals (thereby postulating an immune response to an infective agent), but we could not confirm these results.²⁵ We have found, however, decreased numbers of suppressor T lymphocytes in a case of acute lepromatous uveitis (in preparation), indicating a possible (intraocular) manifestation of erythema nodosum leprosum.

We have failed to confirm that HBV, at least in this country, plays any part in the aetiology of AAU. It is hoped that developments in the field of immunoregulation will increase our understanding of this puzzling condition.

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