Liver disease and the e antigen in HBsAg carriers with chronic renal failure

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SUMMARY This study was undertaken to assess the frequency of development and the stages of evolution of chronic liver disease in patients with renal failure who are chronic carriers of hepatitis B surface antigen. Cirrhosis or chronic active hepatitis developed in five of 21 patients and could not be predicted by the initial histological appearance or by HLA-A and B typing but was associated with the e antigen in four of the five patients. However, the antigen was not a consistent indicator of a poor prognosis, as the four other e antigen positive patients did not develop chronic liver disease during the period of the study. Transmission of hepatitis B to spouses occurred in four cases, was fatal in one instance, and was associated with e antigen in three of the four. Determination of e antigen status in renal unit patients who are carriers of hepatitis B surface antigen may be of value to the patient and his home environment.

Hepatitis has been recognised as a hazard in renal dialysis units since 1965 and its association with hepatitis B surface antigen (HBsAg) was recognised in 1968. However, there have been few systematic studies of the state of the liver in patients with renal failure who are chronic carriers of HBsAg. We report here such a study, which draws attention to the frequent occurrence of chronic liver disease in such patients, to the association between the hepatitis B e antigen and chronic liver disease, and to the danger which e antigen positive patients pose to their home environment.

Methods

PATIENTS

During the period of the study, 1972-77, the prevalence of HBsAg in the 141 patients who received renal transplants was 16%, while 6% of the 181 patients on maintenance haemodialysis were HBsAg positive at some time. Of the total HBsAg positive group of 33 patients, 27 were eligible for study by virtue of being HBsAg positive on monthly testing for six months or longer. Of this group 21 were studied, 17 with functioning renal transplants receiving prednisolone and azathioprine and four on maintenance haemodialysis. In the remaining six, either biopsy was declined or the patient was dead and serum no longer available. The initial histological assessment was by liver biopsy followed by one or more subsequent biopsies over an average period of three years (12 patients) or by necropsy two weeks to 18 months after the initial biopsy (five patients). Four patients had a single biopsy only. Informed consent was obtained from each patient included in the study.

Monthly serum biochemistry and tests for HBsAg and anti HBs were carried out in all patients for a mean of 37 months (range six to 80 months). Tests for e antigen and anti e became available in 1976. They were done on stored serum samples taken at the time of the first biopsy and repeated in many patients but could not be done in one patient from whom serum was not available.

TECHNIQUES

All biopsies were studied using haematoxylin and eosin stains, a reticulin stain, Masson's trichrome stain, orcein stain according to Shikata and Perl's Prussian blue reaction. Biopsies were read blind and were allocated to one of the following diagnostic categories:

- Non-specific hepatitis (NSH) Sparse focal necroses
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and a variable infiltrate of mononuclear inflammatory cells within portal areas;

*Acute hepatitis (AH)* Focal necroses or small areas of confluent necrosis, portal and lobular inflammatory infiltrate, frequent hepatocytes showing eosinophilic degeneration as well as variable numbers of liver cells showing ballooning degeneration.

*Chronic persistent hepatitis (CPH)* Only minor intralobular histological changes, variable prominence of Kupffer cells and a mononuclear inflammatory infiltrate confined to portal areas;

*Chronic active hepatitis (CAH)* Piecemeal necrosis and significant parenchymal and connective tissue involvement.

*Cirrhosis (C)* Fibrosis with disturbance of normal architecture and definite nodule formation.

HBsAg and anti-HBs were sought by radioimmunoassay with confirmation of positive results (Austria II, Abbott Laboratories). The e antigen and anti-e were detected in sera concentrated three-fold against Lyphogel by counter electrophoresis in 0.9% agarose gel10 with 2% dextran (Dextran T250, Pharmacia, M.W. 250,000) and 0.1% protamine sulphate at 10 mA for two hours. Plates were read daily for five days and precipitin lines were stained with Coomassie blue. Positive results were confirmed by immunodiffusion in the same gel or by specific neutralisation of e or anti-e in the test serum with reference anti-e or e reagents. The reference sera were kindly checked by Dr. Ian Gust, Fairfield Infectious Diseases Hospital, Melbourne. HLA A and B locus typing was done by the NIH standard microcytotoxicity technique.11

**Results**

Seven of the 21 patients developed chronic liver disease during the study (group A, Table). From an initial histological diagnosis of AH (four patients) or NSH (three patients), four patients progressed to cirrhosis, one to CAH and two to CPH. Five of the seven patients were e antigen positive, none had anti-e.

The remaining 14 patients (group B, Table) have so far not developed chronic liver disease as judged by histological criteria in nine patients or on clinical and biochemical grounds in five patients; the abnormal liver function tests having resolved in case 8. The initial biopsy had shown AH in three patients, NSH in nine, and fatty change or no abnormality in the remaining two patients. Four

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<th>Table</th>
<th>Clinical and laboratory data in chronic carriers of HBsAg</th>
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Group B—no progression to chronic liver disease during period of observation

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<th>Subsequent histology</th>
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patients in group B had e antigen and one had anti-e.

Acute hepatitis was evident clinically in only four of the eight patients in whom this was the histological diagnosis. Two were on maintenance haemodialysis; in the six transplant recipients immunosuppression had been continuous for a period from one to six years.

The histological data are summarised in the Table and representative cases are illustrated in Figs 1–4. Orcein positive ground glass hepatocytes were found in variable numbers in the initial biopsy in nine patients. Their presence was not related to severity of liver disease or progression to chronic liver disease.

Thus, of 21 patients studied, 14 had mild liver disease, two had CPH, while one developed CAH and four cirrhosis. The e antigen was detected in all but one of the five patients with CAH or cirrhosis. A further five patients were e antigen positive but showed only CPH, NSH, or fatty change and remained stable during the study. One patient only had anti-e; two liver biopsies three years apart showed mild NSH.

Liver function tests were protractedly abnormal at some time during the study in six of the 21 patients and two of them (cases 17 and 18) died in liver failure. Five (cases 1, 8, 11, 18, 19) had biochemical hepatocellular damage and one (case 17) cholestasis.

The distribution of HLA A and B locus antigens was similar in patients who developed chronic liver disease and in those who did not; in particular, there was no increase in HLA A1, B8, or B12 singly or in combination in the former, nor could an association be demonstrated between the presence of e antigen and any individual HLA-A or B locus.

Four spouses of patients developed hepatitis B during the course of the study, and one died. Three of the four patients were e antigen positive. Hepatitis did not occur in other household contacts.

Discussion

The risk of the development of chronic liver disease in patients with renal failure who are chronic carriers of HBsAg is high – nine of 15 patients in the series of Galbraith et al. and seven of 21 in the present group. It occurred in both graft recipients and in patients on maintenance haemodialysis. In the event that treatment of the HBsAg carrier

Fig. 1 Case 3. First biopsy: non-specific hepatitis. There are numerous ground glass hepatocytes and occasional focal necroses. This patient showed an almost identical picture in the second biopsy.

Fig. 2 Case 10. (a) First biopsy: non-specific hepatitis with occasional focal necrosis. (b) Post-mortem: three years after his first biopsy (a) this patient had an established micronodular cirrhosis. Both H and E, x 125 (original magnifications).
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Fig. 3 Case 18. First biopsy: fulminant acute hepatitis with submassive necrosis. In the middle of picture there is a central vein and a small bile duct is visible in the right top corner. The intervening liver substance is necrotic. This patient died a few weeks later in liver failure. H and E, x320 (original magnifications).

state, for instance with interferon\textsuperscript{12} or interferon inducers\textsuperscript{13}, proves successful it would be useful to be able to identify those patients who are particularly likely to develop chronic liver disease. As shown both by this study and by Fauerholdt et al.\textsuperscript{14}, liver biopsy does not have this predictive value. Nor can the occurrence of HLA-A1 or B8 singly or in combination be used to identify the high risk group. In our patients, these antigens were distributed similarly among patients with and patients without cirrhosis and chronic active hepatitis, confirming a previous report\textsuperscript{15} despite the frequent\textsuperscript{16,17} though not uniform\textsuperscript{18} association between HB\textsubscript{A}Ag negative chronic active hepatitis and HLA-B8. A previous survey has shown a negative association between the HLA-A1, B8 phenotype and the HB\textsubscript{A}Ag carrier state\textsuperscript{19}, but this was not so in the present group.

The e antigen, on the other hand, was present in four of the five patients with cirrhosis or chronic active hepatitis, but the association was not statistically significant. Counter electrophoresis, used in this study, is more sensitive than immunodiffusion\textsuperscript{10} but nevertheless a fairly primitive technique. Radioimmunoassay and a longer follow-up than in this series may show whether or not the association is real. The e antigen, first described by Magnus and Espmark\textsuperscript{20} in 1972, tends to be associated with development of chronic liver disease after acute hepatitis B\textsuperscript{21,22}, with the presence of chronic liver disease in HB\textsubscript{A}Ag carriers\textsuperscript{23} and with more severe disease in HB\textsubscript{A}Ag positive chronic active hepatitis\textsuperscript{24}.

The presence of e antigen also serves as a warning to household contacts. Three of the four patients whose spouses developed hepatitis B were e antigen positive. The risk of hepatitis B appears to be confined to spouses\textsuperscript{25}, and this was also the case in the present study. In view of the one fatality, regular administration of HB hyperimmune globulin appears justified to a spouse who is also a sexual partner of an e antigen positive patient and who has no serological evidence of past HBV infection. Routine determination of e antigen status in HB\textsubscript{A}Ag positive renal unit patients also seems advisable.

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