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HB_eAg and anti-HB_e in acute and chronic liver diseases

B.N. Tandon, Leela Krishnamurthy, and B.M. Gandhi

Department of Gastroenterology, All-India Institute of Medical Sciences, New Delhi.

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A total of 142 serum samples were screened for HB_eAg and anti-HB_e, using an immunodiffusion method. The sera were collected from 85 patients of acute viral hepatitis, 26 of chronic active hepatitis and active cirrhosis, 8 of fulminant hepatitis, 3 each of subacute hepatitis and chronic persistent hepatitis, 6 of inactive cirrhosis, one of hepatoma and 10 from asymptomatic carriers of HB_sAg. There was a high association of HB_eAg (31 per cent) with chronic active hepatitis and cirrhosis. In acute hepatitis, not only the presence but persistance of HB_eAg proved to be significant in predicting progression to chronic liver disease. A large proportion of asymptomatic carriers (60 per cent) had anti-HB_e.

Since its discovery[1] in 1972, the clinical significance of the e-antigen antibody system of virus B hepatitis has been under study by several investigators[2-7].A review of the literature on this subject brings forth the following facts :

HB_eAg positive acute hepatitis is associated with a higher incidence of the sequelae of chronic hepatitis[2-4,7] and carrier state. Biochemical and morphological evidence of chronic liver disease is more frequent among HB_eAg positive carriers than among HB_eAg negative[4,6]. Chronic active hepatitis[3,4,5] and active cirrhosis are associated with a high positivity for HB_eAg than is inactive cirrhosis[4]. HB_eAg and anti-HB_e do not occur in the same patient. Antibody to HB_e does not have a bad prognostic significance and is generally equated with complete recovery in acute viral hepatitis[3,4]. HB_eAg positivity is associated with DNA polymerase activity and an abundance of Dane particles[8-11], suggesting the infective potential of the sera.

The present study was carried out to evaluate the significance of the 'e' system in acute and chronic liver diseases, especially in relation to progression of acute to chronic hepatitis.

Material and Methods

Patients : Sera collected from 142 patients of liver disease, attending the gastroenterology service of the All-India Institute of Medical Sciences between January 1976 and March 1978, were studied. These included sera from 85 patients of acute viral hepatitis (AVH 53 HB_sAg positive and 32 negative), 8 from fulminant hepatitis, 3 of subacute hepatitis, 26 chronic active hepatitis (CAH) and active cirrhosis, 3 chronic persistent hepatitis (CPH), 6 inactive cirrhosis, 1 of hepatoma and 10 of asymptomatic carriers of HBAg.

Sera of all the patients were tested at the first visit and subsequent sera were examined serially in 26 patients of acute virus B hepatitis. These included 6 patients of AVH, who had shown persistence of clinical, biochemical and morphological abnormalities at the end of six months and evidence of progression to chronic hepatitis. Serial samples were also examined in patients with persistent HB_sAg antigenemia. Six-monthly samples of sera of patients of chronic active hepatitis and active cirrhosis were also examined during their follow up. The diagnosis of acute viral hepatitis, chronic active and chronic persistent hepatitis was established according to the criteria agreed by the expert group of the Indian Council of Medical Research[12]. Standard criteria were adopted for the diagnosis of fulminant hepatitis[13] and subacute hepatitis[14].

Method : The procedure followed for testing HB_eAg and anti-HB_e, was NIH's modification of Le Bouvier's immunodiffusion method (Le Bouvier, G., personal communication). Immunodiffusion was carried out using 0·8 per cent agarose in Tris (0·05 *M*)—saline (0·015 *M*) buffer pH 7·6, with 0·1 per cent sodium azide. 2·0 ml of agarose was added to a slide (1 × 3 inch) and the prepared slides were allowed to harden overnight in the cold. The test pattern is shown in the Figure. Wells were 3 mm diameter at 3 mm distance from each other at the edges. The additional wells filled with diluent prevented outward diffusion of the reactants. All the standard wells were filled twice and the sample wells three times during the first few hours. The slides were read after 48-72 h and periodically up to one week. Precipitin lines were read under indirect illumination using a magnifying lens. Standard sera containing HB_cAg and anti-HB_e were obtained from the NIH, Bethesda, U.S.A. All the test sera were concentrated three to four-fold, using polyethylene glycol. Sample 5 in the figure was positive for anti-HB_e while sample 4 was HB_eAg positive.

HB_sAg was detected by counter immunoelectrophoresis.

Results

The results are summarised in Table I. All the 32 patients of AVH were negative for HB_sAg or anti-HB_e. Ten (19 per cent) of the 53 patients of virus B hepatitis were positive for HB_eAg and six (11 per cent) were positive for anti-HB_e (Table I). Serial estimation of HB_eAg for 2-6 months in 7 of these ten patients revealed persistence of HB_eAg in 4 and loss of HB_eAg in three. Of the former four, two were in the stage of prolonged hepatitis, one had become a carrier of HB_sAg while the fourth patient had progressed to subacute hepatitis. The asymptomatic carrier subsequently showed presence of anti-HB_e. All the 3 patients who lost HB_eAg recovered completely although two of them had a prolonged course of illness lasting for more than ten weeks.

All the six patients of acute viral hepatitis who were positive for anti-HB_e, showed complete recovery. Thirty-seven patients with virus B hepatitis had neither HB_eAg nor Anti-HB_e and all but three recovered. One patient in this group had a prolonged recovery and two others progressed to CAH. They were both persistently positive for HB_sAg during the follow up (Table II).

Fig. Test pattern of immunodiffusion used in the detection of HB_eAg and anti-HB_e 1-8, Test samples; X, Buffer; A, Standard antigen; B, Standard antibody.

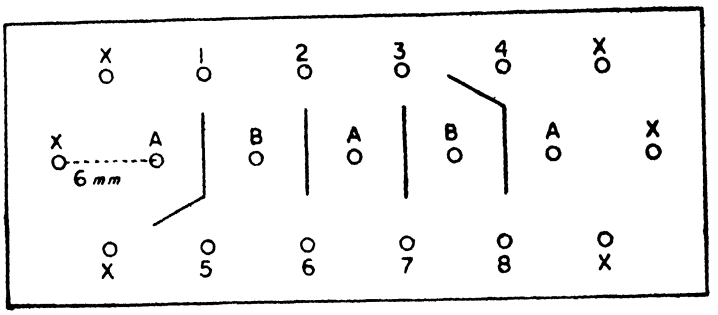

Table I. Frequency of HB_eAg and anti-HB_e in acute and chronic liver diseases and carriers of HB_eAg

Diagnosis	No. studied	HB_eAg positive		Anti-HB_e positive	
		No.	%	No.	%
Acute viral hepatitis					
HB_s+ve	53	10	19	6	11
HB_s—ve	32	0	0	0	0
Fulminant hepatitis	8	1	12	0	0
Subacute hepatitis	3	1	33	0	0
Chronic active hepatitis and active cirrhosis	26	8	31	4	15
Carriers	10	1	10	6	60
Total	132	21	16.7	16	12

Table II. Follow up of $_eAg$—Ab system positive and negative patients of acute virus B hepatitis

'e' antigen-antibody status	Total No.	Prolonged hepatitis (>6 weeks)	Subacute hepatitis	Chronic active hepatitis	Asymptomatic carriers	Recovered
'e' Ag+ve	7	2	1	0	1*	3
'e' Ab+ve	6	0	0	0	0	6
'e' Negative	37	1	0	2**	0	34

*Patient subsequently sero-converted to Anti-HB_e but continued to carry HB_sAg.
**One patient succumbed to CAH.

Of the eight patients with fulminant hepatitis, only one was positive for HB_eAg. This patient succumbed to the disease. One patient of subacute hepatitis continued to have persistent HB_sAg and HB_eAg for over four months.

HB_sAg and anti-HB_e were positive respectively in 31 per cent and 15 per cent of patients with chronic active liver disease. None of the three patients of chronic persistent hepatitis (CPH) had either HB_eAg or its antibody. Of the six patients of inactive cirrhosis, none had HB_eAg, while one showed the presence of anti-HB_e. A single patient of hepatoma was studied and he was HB_eAg positive.

Anti-HB_e was detected in 6 of the 10 HB_sAg carriers, while HB_eAg was present in only one.

Discussion

The results of the present study demonstrated a frequent association of HB_eAg with two types of chronic active liver diseases *viz.* chronic active hepatitis and cirrhosis of the liver with activity. This observation confirms the earlier reports from Sweden[2], Denmark[3], England[4] and the U.S.A.[7]. Patients with chronic but inactive type of liver disease *viz.* chronic persistent hepatitis and cirrhosis of the liver without activity did not have positive HB_eAg. Western authors[2,4,7,15] have reported HB_eAg positivity rate of 0 to 46 per cent in patients with these liver diseases. Diagnosis of 'activity' in a liver biopsy sample may be missed due to sampling error and this may account for differences in different series.

The clinical course of HB_eAg positive acute viral hepatitis in the present study was characterised by a delayed resolution in 2 patients, compilation of subacute hepatitis and carrier state in one each. Follow up has not been long enough to allow us to comment on the frequency of chronic hepatitis in this group of patients. Compilation of chronic hepatitis has been recorded in more than 50 per cent of the patients of HB_eAg positive acute viral hepatitis[2,3,7]. The present study further suggests that persistence of HB_eAg and not just its detection in the initial stage of acute viral hepatitis, is associated with high frequency of chronic sequelae. Thamer and associates[16] also reported a similar prognostic significance of HB_eAg.

HB_eAg was positive in one of the 10 asymptomatic carriers of HB_sAg. Frequency of HB_eAg in asymptomatic carriers in western countries is reported[4,15,17] to be 0-26 per cent. It has also been reported that presence of HB_eAg in asymptomatic carriers is associated with higher frequency of abnormal liver function test and histological changes, on liver biopsy[5,18].

Presence of antibody to 'e' antigen and seroconversion to anti-HB_e was found to be associated with good prognosis in viral hepatitis. This has been also emphasised by other investigators in the field[2,4,6].

The significance of 'e' Ag-antibody system in fulminant hepatitis, subacute hepatitis and hepatoma is not clear. Some association of anti-HB_e with hepatoma has been reported by Eleftheriou and co-workers[4]. There are no reports in the literature of studies of 'e' Ag-antibody system in subacute and fulminant hepatitis. Frequency of HB_eAg positivity in subacute hepatitis was the same as in chronic active hepatitis in the present

series. Only one patient with fulminant hepatitis (12 per cent) was positive for HB_eAg. All the patients with fulminant and subacute hepatitis were negative for antibody to 'e' Ag.

References

1. Magnius, L.O. and Espmark, J.A. A new antigenic complex co-occurring with Australia antigen. *Acta Pathol Microbiol Scand* (B) **80** (1972) 335.
2. Nokrans, G., Magnius, L.O. and Iwarson, S. 'c' Antigen in acute hepatitis B. *Br Med J* **1** (1976) 740.
3. Nielson, I.O., Dietrichsen, O. and Juhl, E. Incidence and meaning of the 'e' determinant among hepatitis B antigen positive patients with acute and chronic liver disease. *Lancet* **ii** (1974) 913.
4. Eleftheriou, N., Thomas, H.C., Heathcote and Sherlock, S. Incidence and clinical significance of 'e' antigen and antibody in acute and chronic liver diseases. *Lancet* **ii** (1975) 1171.
5. Feinman, S.V., Berris, B., Sinclair, J.C., Wrobel, D.M., Murphy, B.L. and Maynard, J.E. e-Antigen and anti-e in HB_sAg carriers. *Lancet* **ii** (1975) 1173.
6. Aikawa, T., Sairenji, H., Furuta, S., Kiyosawa, K., Shikata, T., Imai, M., Miyakawa, Y., Yanase, Y. and Mayumi, M. Seroconversion of hepatitis B e-antigen and Anti-HB_e in acute hepatitis B virus infection. *N Engl J Med* **298** (1978) 439.
7. Fay, O., Tanno, H., Renoroni, H., Edwards, V.M., Mosley, J.W. and Redeker, A.G. Prognostic implication of e-antigen of hepatitis B virus. *JAMA* **238** (1977) 2501.
8. Nordenfelt, E. and Andren Sandberg, M. Dane particle associated DNA polymerase and e-antigen. Relation to chronic hepatitis among carriers HB_sAg. *J Infect Dis* **134** (1976) 85.
9. Takahashi, K., Imai, M., Tsuda, F., Takahashi, T., Miyakawa, Y. and Mayumi, M. Dane particle and e-antigen. *J Immunol* **117** (1976) 102.
10. Shikata, T., Karasawa, T., Abek, Uzawa, T.. Susaki H., Oda, T., Imai, M., Mayumi, M. and Moritsuau, Y. Hepatitis B e-antigen and infectivity of hepatitis B. *J Infect Dis* **136** (1977) 571.
11. Alter, H.J. Seeff, L.B., Kaplan, P.M., Auliffe, V.J., Wright, E.C., Gerin, J.L., Purcell, R.H., Holland, P.V. and Zammerman, H.J. Type B hepatitis. The infectivity of blood positive for e antigen and DNA polymerase after accidental needle stick exposure. *N Engl J Med* **295** (1976) 909.
12. Indian Council of Medical Research. Minutes of the meeting of the expert group on liver disease held at ICMR, New Delhi on 7-8th Dec., 1976.
13. Trey, C. *The Fulminant Hepatic Faiiure Surveillance Study in Liver.* Eds. S.J. Saunders and J. Terblanche, (Pitman Medical London) 1973, p 120.
14. Tisdale, W.A. Subacute hepatitis. *N Engl J Med* **268** (1963) 85, 138.
15. El Sheikh, N., Woolf, I.L., Galbraith, R.M., Eddleston, A.L.W.F., Dymock, I.W. and Williams, R. e Antigen-antibody system as an indicator of liver damage in patients with hepatitis B antigen. *Br Med J* **4** (1975) 252.
16. Thamer, G., Gmelin, K. and Kommerell B. e Antigen. Prognostic marker in acute viral hepatitis B. *Lancet* **ii** (1976) 577.
17. Smith, J.L., Maynard, J.E., Schalm, S.S., Summerskill, W.H.J. and Gitnick, G.L. Studies of e antigen in acute and chronic hepatitis. *Gastroenterology* **71** (1976) 208.
18. Magnius, L.O., Lindholm, A., Lundin, P. and Iwarson, S. A new antigen-antibody system. Clinical significance in long term carriers of hepatitis B surface antigen. *JAMA* **231** (1975) 356.

Reprint requests : Dr. B.N. Tandon, Professor of Medicine, Head of the Department of Gastroenterology and Human Nutrition, All-India Institute of Medical Sciences, Ansari Nagar, New Delhi-110016.