DURATION OF HEPATITIS B SURFACE ANTIGENAEMIA AND ITS CORRELATION WITH THE HISTOPATHOLOGICAL AND CLINICAL OUTCOME IN ACUTE AND CHRONIC HEPATITIS

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SUMMARY. The persistence of Hepatitis B surface antigen (HBsAg) in 156 patients with histopathologically proven acute viral hepatitis and 27 patients with chronic active hepatitis was assessed and correlated with their clinical and histopathological outcome; 1387 sequential serum samples were tested for HBsAg and its antibody (anti HBs). In the group with acute viral hepatitis, 86% of the patients who recovered, 67% of the patients who deteriorated histopathologically and 67% of the fatal cases carried HBsAg for up to 8 weeks only. While 56% of patients with chronic active hepatitis harboured HBsAg for 13–80 weeks, only 10% of the group with acute viral hepatitis did so. Of patients with chronic active hepatitis 37% deteriorated to cirrhosis and 11% died. Diverse anti-HBs-response patterns are reported and may have clinical significance.

INTRODUCTION

Since the dramatic incident when Barbara Werner diagnosed herself by the Australia antigen test as the first case of hepatitis in Blumberg's laboratory (Blumberg, 1975), methods and techniques proliferated (WHO, 1970) for analysing every aspect of hepatitis B. One of the analytical approaches was to follow the course of hepatitis B surface antigenaemia in patients with various liver diseases, which not only revealed sequential serological events (Melnick, Dreesman and Hollinger, 1976) but also demonstrated biochemical, histopathological and clinical characteristics (Almeida and Waterson, 1975).

The present study was undertaken to determine the duration of carriage of hepatitis B surface antigen (HBsAg) in the serum of patients with histopathologically diagnosed acute viral hepatitis and chronic active hepatitis to correlate antigenaemia with the histopathological and clinical outcome. The work was done in the Institute of Microbiology in collaboration with the Departments of Pathology and Gastroenterology, Madras Medical College during 1975–1979.

MATERIALS AND METHODS

One hundred and fifty six patients with HBsAg-positive acute viral hepatitis and 27 patients with HBsAg-positive chronic active hepatitis were studied immunologically, histopathologically and clinically for periods up to 80 weeks.

Screening for HBsAg and its antibody (anti HBs) was done by the counterimmuno-electrophoresis method of Pesendorfer, Krassnitsky and Wewalka (1970). Histopathology of the liver was studied by percutaneous needle biopsy (Anderson and Kissane, 1977). Patients' physical well being and clinical features were assessed and the clinical outcome was recorded.

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As a policy blood samples were taken once a week and we adhered to this procedure as strictly as possible. Thus 1387 sequential serum samples were analysed for HBsAg and anti HBs. Initial liver biopsies were done and further biopsies were taken when desirable and possible.

RESULTS

A total of 183 patients with acute and chronic liver diseases were followed for at least 80 weeks (table I). HBs antigenaemia had cleared from 63% of cases of acute viral hepatitis within the first 4 weeks, but from only 26% of cases of chronic active hepatitis. Among the remaining cases of chronic active hepatitis, 11% were HBsAg-positive for up to 8 weeks; the antigenaemia cleared within 9–12 weeks in 7% and 33% of cases remained HBsAg-positive for 13–24 weeks. Interestingly, two cases had prolonged antigenaemia, one up to 55 weeks and the other up to 72 weeks. Although antigenaemia cleared within a month in most cases of acute viral hepatitis, 15% were HBsAg-positive for 9–36 weeks and in two patients, antigenaemia persisted for a year and for > 5 years. (This last patient was a lifetime convict in the Madras Central prison and was a fertile and accessible source of HBsAg in this study).

When the clinical and histopathological outcome of the 156 cases of HBsAg-positive acute viral hepatitis was analysed (table II), it was found that 86% of the patients who recovered, 67%

TABLE I

Duration of HBs-antigenaemia in acute viral hepatitis and chronic active hepatitis

Duration of HBs-antigenaemia (in weeks)	Number (percentage) of patients and mean duration of HBs-antigenaemia in			
	Acute viral hepatitis (156 cases)	Mean $\pm$ SD (in weeks)	Chronic active hepatitis (27 cases)	Mean $\pm$ SD (in weeks)
1–4	99 (63)	2.70 $\pm$ 1.04	7 (26)	2.96 $\pm$ 0.83
5–8	32 (20)	6.47 $\pm$ 1.14	3 (11)	6.33 $\pm$ 1.25
9–12	9 (6)	10.78 $\pm$ 1.13	2 (7)	10.50 $\pm$ 0.50
13–24	9 (6)	18.33 $\pm$ 3.02	9 (33)	18.22 $\pm$ 4.69
25–36	5 (3)	30.40 $\pm$ 3.26	4 (15)	32.00 $\pm$ 3.54
37–55	1 (1)	51.00	1 (4)	55.00
56–80	1 (1)	80.00	1 (4)	76.00

TABLE II

Duration of HBs-antigenaemia and histopathological and clinical outcome in acute viral hepatitis

Duration of HBs-antigenaemia (in weeks)	Number (percentage) of patients in whom the given outcome occurred					
	Total	Recovered	Progressed to			Died
			CPH	CAGH	CIRR	
1–4	99	92 (93)	0	2 (2)	2 (2)	3 (3)
5–8	32	29 (91)	1 (3)	1 (3)	0	1 (3)
9–12	9	7 (78)	0	0	1 (11)	1 (11)
13–24	9	7 (78)	1 (11)	0	0	1 (11)
25–36	5	5 (100)	0	0	0	0
37–55	1	1 (100)	0	0	0	0
56–80	1	0	1 (100)	0	0	0
Total	156	141 (90)	3 (2)	3 (2)	3 (2)	6 (4)

CPH = Chronic persistent hepatitis; CAGH = Chronic aggressive hepatitis; CIRR = Cirrhosis of liver.

of the patients who deteriorated histopathologically and 67% of the cases who died had detectable HBsAg in their blood for <8 weeks. Even when antigenaemia persisted for 80 weeks or more, only a minority of the cases progressed to chronic persistent hepatitis, chronic aggressive hepatitis and cirrhosis and 33% of cases died.

The pattern was reversed in 27 cases of chronic active hepatitis. None made a complete clinical and histopathological recovery. Half (52%) of them remained histopathologically unchanged, 37% deteriorated to develop cirrhosis and 11% died. It is also clear from table III, that in chronic active hepatitis both clinical improvement and the absence of histopathological deterioration were inversely proportional to the duration of antigenaemia—the longer the period of HBsAg positivity, the less were the chances of a favourable outcome.

There were different patterns of anti-HBs response in the groups studied (table IV). The majority of the anti-HBs-positive cases analysed (15 out of 28) became anti-HBs positive after HBsAg had been present and then disappeared from the blood; anti HBs appeared either immediately or after an interval (Group A). The interval was 1–32 weeks (mean $\pm$ SD = 8.7 ± 10.04) in acute viral hepatitis and 7–12 weeks (9.5 ± 2.5) in chronic active hepatitis. Group B included seven patients in whom anti HBs was detected simultaneously with HBsAg. In this group, antigen and antibody co-existed for a maximum of 4 weeks. The other types of anti-HBs response included initial anti-HBs positivity followed by HBsAg with or without a break (Group C—3 cases) and alternating HBsAg, anti HBs positivity (Group D—3 cases). It is interesting to note that all the patients with liver disease who were anti-HBs positive survived except two (one acute and one chronic) cases who had HBsAg alternating with anti-HBs and ultimately died.

TABLE III

Duration of HBs-antigenaemia and histopathological and clinical outcome in chronic active hepatitis

Duration of HBs-antigenaemia (in weeks)	Number (percentage) of patients in whom the given outcome occurred				
	Total	Unchanged	Progressed to		Died
			CPH—CAgH	CAH—CIRR	
1–4	7	5 (72)	0	1 (14)	1 (14)
5–8	3	2 (67)	0	1 (33)	0
9–12	2	0	1 (50)	0	1 (50)
13–24	9	5 (56)	0	3 (33)	1 (11)
25–36	4	2 (50)	0	2 (50)	0
37–55	1	0	0	1 (100)	0
56–80	1	0	0	1 (100)	0
Total	27	14 (52)	1 (4)	9 (33)	3 (11)

CPH = Chronic persistent hepatitis; CAgH = Chronic aggressive hepatitis; CAH = Chronic active hepatitis; CIRR = Cirrhosis.

DISCUSSION

When the duration of HBs antigenaemia was correlated with histopathological findings in patients with acute viral hepatitis, 78% of the patients who deteriorated histologically and 83% of the fatal cases had antigenaemia for up to 12 weeks. In chronic active hepatitis, 30% of the cases with progressive histopathological changes were HBsAg positive for 12 weeks and the rest for up to 80 weeks. Two of the three fatal cases in this group had HBsAg for less than 3 months. However, Dietrichson and Neilson (1975) followed up 500 patients by the counterimmuno-electrophoresis method and found that all the patients with chronic liver disease carried HBsAg for > 13 weeks. Iwarson and Norkrans (1975) used the same method and showed that 4.4% of their 440 patients with hepatitis B had HBs antigenaemia for > 3 months.

The shorter duration of antigenaemia in the majority of the patients in the present series might be due to either a greater length of time between the onset of the illness and the first test for

HBsAg or due to the less sensitive technique employed for HBsAg detection. In the light of the association of HBeAg with infectivity and bad prognosis (WHO, 1977), the deterioration that occurred in many of our patients could also be due to a higher rate of HBeAg positivity as already reported (32% in acute viral hepatitis and 50% in chronic active hepatitis; Thyagarajan *et al.*, 1980). However as HBeAg is found in those with high to moderate titres of HBsAg one would expect the HBsAg to persist longer in the HBeAg-positive patients. In the absence of a follow-up test for HBeAg and a more sensitive technique for HBsAg detection, it is suggested by the present study that there is a contest between the host and the parasite (Hepatitis B virus) which might result in either complete recovery or clinical and histopathological deterioration within a maximum period of 12 weeks.

In the present series, 6% of the HBsAg-positive cases of viral hepatitis progressed to chronic liver disease and 37% of the cases of chronic active hepatitis deteriorated to cirrhosis (tables II and III) whereas 10% of cases of hepatitis B progressed to chronic liver disease in the series by Iwarson and Norkrans (1975). Redeker (1975) found that 3% of cases of acute viral hepatitis became chronic. The long term follow-up in our series has revealed two patients amongst the acute group who carried HBsAg for 12–63 months whereas six patients had HBsAg for 14–73 months in Redeker's series, a comparable pattern.

A death rate of 4% in acute viral hepatitis and 11% in chronic active hepatitis is a matter of the utmost concern. However the clinical complications in some of these cases may have enlarged the figures.

The anti-HBs response in patients with liver disease who were followed up showed a variety of patterns (table IV) as did the rate of HBsAg carriage. Such a diverse pattern of anti-HBs response has been observed by Zuckerman *et al.* (1975) in rhesus monkeys. Furthermore it is of immunological interest as to why the group with alternating HBsAg–anti HBs positivity alone should die while all the others in the groups who became anti-HBs positive survived. A demonstration of the HB virus, and its markers and immune complexes *in situ* in such cases might possibly offer an explanation for this observation.

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