Original Articles

HEPATITIS BS ANTIGENEMIA—ROLE IN THE EPIDEMIOLOGY OF LIVER DISEASE

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Abstract

One thousand two hundred asymptomatic individuals were screened for the presence of hepatitis Bs antigen. Out of 44(3.6%) who revealed its presence, 39 were investigated further. The majority of carriers (59%) had at least one abnormal liver function test. Liver biopsy was evaluated in 35 cases. All had some disturbance of liver morphology. In 20 (55%) the changes were consistent with viral hepatitis. The remaining had nonspecific and reactive histological features. Three carriers developed episodes of jaundice during the follow up period. The widespread antigenemia and the incidence of hepatitis in carriers indicates that HBs antigen plays a key role in the epidemiology of liver disease. A large reservoir of anicteric hepatitis due to antigen carriers exists. This reservoir could be a significant factor in the spread of infection as well as in the causation of sporadic icteric hepatitis and chronic liver disease in Pakistan.

HBs antigenemia is considered to be a maker of infection with Hepatitis B virus. Its incidence in the general population in Europe and North America is insignificant. On the other hand in many developing countries where the socio-economic and hygienic standards are low, a large number of people carry the antigen without suffering from any obvious diseases.

Although these carriers rarely pose a clinical problem, the possibility that they play a significant role in the epidemiology of liver disease has to be seriously considered. The studies which have so far been carried out to evaluate hepatic status in these cases have yielded conflicting results. While some investigators have failed to find unequivocal evidence of acute hepatitis (Reinicke et al., 1972; Klinge et al., 1971) others have reported a variety of lesions ranging from hepatitis to cirrhosis (Griffin et al., 1973; Singleton et al., 1971; Anderson et al., 1974; Prince et al., 1969). The role of antigenemia has, therefore, remained equivocal.

We present here results of a study undertaken to determine hepatic status in asymptomatic

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people with HBs antigenemia and to assess its role in the epidemiology of liver disease in the population.

Material and Methods:

One thousand two hundred apparently healthy individuals were screened. Eight hundred of these were new recruits from various regions of the country who had reported for their basic training in the training establishments of the Armed Forces. They were examined within 4-6 weeks of their arrival. The remaining four hundred were in service from 1 to 16 years (mean 5 years). The mean age of recruits was 18.5 years (range 16-19 years) while those in service were slightly older (mean age 21 years, range 18-42 years). The service in the Armed Forces is purely on voluntary basis.

A physical examination and a blood examination for SGPT, SGOT and HBs antigen (Countercurrent immunoelectrophoresis) was carried out in all individuals. Those showing hepatic enlargement or raised SGOT/SGPT were rechecked after 10 days. If the abnormal findings persisted, they were admitted in hospitals after obtaining their consent for liver biopsy. The individuals who showed the presence of antigen in their sera were also admitted.

While in hospital a complete history with special reference to any previous episodes of jaundice, drug use, injections or malaria was obtained. A biochemical hepatic profile including serum bilirubin, proteins, transaminases, alkaline phosphatase, cephalin cholesterol and thymol turbidity was obtained. This was repeated at weekly intervals during the hospital stay. Blood smears were also examined for atypical lymphocytes and sera were tested for the presence of heterophil antibody. The stools were checked for the presence of intestinal parasites or their ova for five consecutive days. Liver biopsy using Menghini technique was obtained. The slides were stained with haemotoxylin and eosin and for reticulin.

The histological features were interpreted without any information about the clinical or biochemical status of the patients. The carriers are being followed at three monthly intervals.

Results

Forty four out of 1200 individuals were found to have HBs antigenemia. Thirty nine who consented to biopsy were admitted in hospital for further studies. Twenty nine persons who showed sustained rise in serum transaminases or hepatomegaly without antigenemia were also admitted. They are subject of a separate report.

Clinical Features:

The incidence of antigenemia was more frequent in those under 30 years. The mean age of carriers was 20 years (range 16-41 years). 80% were between 16-20 years of age.

All individuals were symptom free except 7, who complained of slight pain in the right hypochondrium on exertion. No history of alcohol intake or drug abuse was elicited. Four gave history of jaundice 3-12 years before admission while 11 had suffered from fever with rigors suggestive of malaria in the previous 6 months. The liver was enlarged 2 cm below the costal margin in 4 subjects. No splenic enlargement or any other stigmata of liver disease were observed.

Laboratory Results:

Nineteen (48.5%) had elevation of one or both transminases. SGPT was raised more frequently than SGOT. Serum alkaline phosphatase was increased in 8(20.0%) and cephalin cholesterol was abnormal (++++) in 20 (51.2%). 41% of carriers had all liver function tests within normal limits while in 38% two or more tests were abnormal.

No abnormal lymphocytes were seen in the peripheral blood and heterophil antibodies were not detected in the sera. The stool examination revealed ova of hookworm in 15, Ascaris in 2, Giardia lamblia in 4 and H.nana in 2 cases.

Histological Features:

Four of the thirty nine biopsies were considered inadequate. The histological changes were generally mild in the remaining 35 cases. They were divided into 2 groups.

Group-I (Hepatitis):

There were labular as well as portal changes in these cases. The lobules showed mild disturbance of radial architecture due to swelling and shrinkage of hepatocytes. Ballooning (Fig. 1) was also seen. Acidophilic Councilman-like bodies were seen in all cases (Fig. 2). Ground glass change of the hepatocytes was noted in 5. Focal intralobular necrosis with replacement of liver cells by lymphocytes and histiocytes was also present in all. 5 cases showed macrophages containing lipofuchsin pigment. The portal changes consisted of mild infiltration by lymphocytes. The limiting plate was intact.

Cholestasis was not present in any case. One patient who developed jaundice showed mild cholestasis in the biopsy carried out during the episodes of jaundice. The previous biopsy in this case was free of cholestasis.

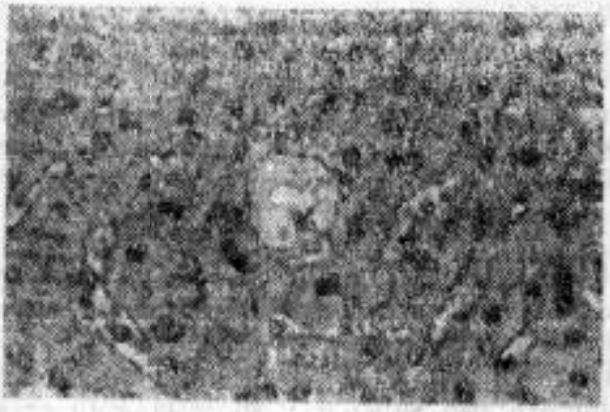

Fig. 1: Group-I. There is loss of radial architecture with ballooning and vacuolation of cells. Ground Glass change in cytoplasm is also present

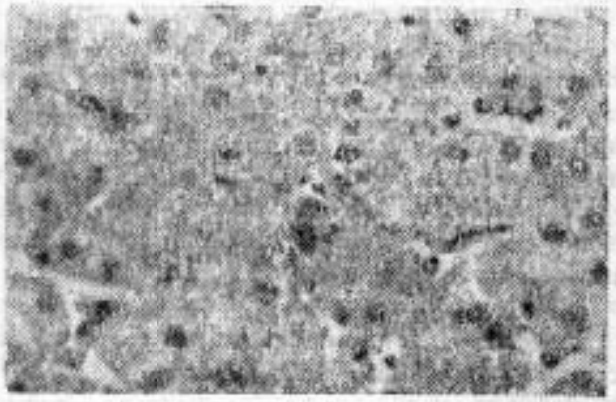

Fig. 2: Group-I. A councilman like body with Kupffer cell hyperplasia.

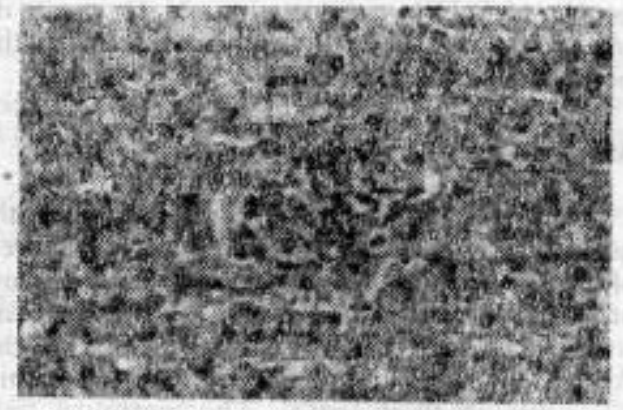

Fig. 3: Group-II. There is mild anisocytosis with focal lobular infiltrate of lymphocytes and histiocytes.

A co-relation of histological groups with laboratory features is given in Table I. In the antigen negative group only 22 showed features of hepatitis.

Follow Up:

These cases have been followed for 6 months to one year at the time of writing this report. The average follow up period is 30 weeks. The majority of individuals with antigenemia, 86% have been found to be chronic carriers (antigenemia over three months).

Three subjects developed jaundice, with symptomatology indistinguishable from that seen in a case of viral hepatitis, during the period of observation. These cases continued to show abnormalities in transaminases and other liver function tests in the period between the detection of antigen and the development of jaundice. Two of these patients showed the presence of antigen before and after the episode of jaundice while one had antigenemia before and in the first week of jaundice. This patient was antigen negative later on.

Table I: Liver Function Tests in Histological Groups

Cases showing Abnormal Results

Histological Group	*Serum Bilirubin*	*Alkaline Phosphatase*	*SGOT*	*SGPT*	*Cephalin Cholesterol*	*Thymol Turbidity*	*cases with two or more abnormal tests*
Group-I (20 cases)	0	8 (40%)	9 (45%)	16 (80%)	13 (65%)	7 (35%)	13 (65%)
Group-II (15 cases)	0	3 (20%)	0	2 (13%)	3 (20%)	0	2 (13%)

3 cases showed hyperbilirubinemia during follow up.

Group-II (Non-Specific Reactive Changes).

The changes in this group were milder. The alteration of architecture was slight. Focal intralobular necrosis with replacement of liver cells by groups of lymphocytes and histiocytes was present in all cases (Fig. 3). Acidophilic bodies, however, were not seen.

The clinical and laboratory features in these cases are presented in Table-II.

Table II: Clinical and Laboratory Features in Carriers with Jaundice

	Case-I	*Case-II*	*Case-III*
Interval between detection of antigen and jaundice	12 weeks	30 weeks	45 weeks
Duration of Jaundice	1 week	3 weeks	4 weeks
Anorexia	(+)	(+)	(+)
Vomiting	(+)	(+)	(+)
Fatigue	(+)	(+)	(+)
Dark Urine	(+)	(+)	(+)
Bilirubin mg/100 ml.	2.5	5.7	10.4
Alk. Phosphatase (K & A) units	25	20	17
SGOT units/ml (Reitman & Frenkel)	475	1100	1260
SGPT units/ml (Reitman & Frenkel)	630	1260	1400
Thymol Turbidity (Mclagen units)	5.3	5.5	6
Cephalin Cholesterol	(++++)	(++++)	(++++)

The level of transaminases in the carriers fluctuated during the follow up period. Out of 24 individuals who had normal enzyme levels initially, 18 did not show any subsequent rise. Of another 12 who had elevated enzymes at the time of detection of antigen, 7 returned to normal. In the remaining 3 individuals the levels were variable.

Discussion

A number of studies have been carried out in recent years to document liver disease in people with HBs antigenemia. However, most of them have been blood donors. This group is not an ideal population for study because it excludes those with history of jaundice and includes, especially in the case of professional donors, many with addiction to hepatotoxic drugs or alcohol. Our cases were drawn from asymptomatic young adults, most of whom had recently arrived from different parts of the country. They perhaps reflect the effects and behaviour of antigenemia in our general population.

The incidence of 3.6% of antigenemia in the symptom free people is fairly high but not unexpected. It compares with 4% reported earlier in a small study in Pakistan (Aziz et al., 1971). The method for detection of antigen available to us was not very sensitive. The real incidence of antigenemia is therefore likely to be higher than indicated by these figures.

The carriers were without any clinical evidence of liver disease. The majority, however, revealed disturbance of liver function as seen by at least one of the commonly used liver function tests. The biochemical abnormalities co-related with the severity of histological changes in these cases.

All carriers showed abnormal liver morphology on biopsy even though the changes were quite mild. Twenty cases in group-I showed hepatitis as revealed by hepatocellular and portal changes. While evaluating the possible etiological factors responsible for this morphology the following features of these cases appeared to be relevant and worthy of consideration.

1. The carriers were apparently healthy young adults without any history or evidence of systemic disease. There was no history of drug abuse or alcoholism.

2. The presence of intestinal parasites did not appear to have any co-relation with the presence or severity of lesions. The possibility of infectious mononucleosis was also excluded.

3. The morphological changes were associated with disturbance of liver function and were within the spectrum accepted to be due to viral hepatitis (Review 1971).

4. Three of the carriers developed typical acute viral hepatitis with jaundice during the period of observation.

Although it is possible that the laboratory and histological features documented in these cases may be due to some as yet unidentified biological agent or toxin, we have been led, both by a process of exclusion as well as from the morphological and biochemical abnormalities observed, to feel that they should be classified as cases of viral hepatitis.

The changes in group-II were non-specific. Because the liver has a very limited range of response to injury, they could be the result of a number of hepatotoxic agents. However, our own studies in late stages of viral hepatitis as well as those of others (Kalk et al., 1947) indicate that they could be sequelae of slowly resolving hepatitis.

It would appear that the presence of antigenemia is associated with a large spectrum of histological and biochemical changes. It is not harmless symbiosis as might be imagined because of widespread prevalence in apparently healthy people. Many of the carriers suffer from a potentially serious disease. The fact that it is not manifested clinically may be due to mildness of infection or host factors.

The carriers also seem to play a very significant role in the epidemiology of liver disease. The prevalence of antigenemia (3.6%) and hepatitis in the carriers (55%) indicates that a large number of people suffer from anicteric hepatitis. A projection of these figures to the entire population of this country (about 62

million) reveals an enormous pool of asymptomatic viral hepatitis (over one million people) due to antigen carriers. These individuals being apparently healthy, can spread the disease by close personal contact and through body secretions far more easily than a sick individual could. A number of vectors such as mosquitoes, bedbugs (Brotman et al., 1973) and some other as yet unknown agents may also be involved in spreading the antigenemia and consequently hepatitis. The presence of hookworms in a large percentage of our cases could be significant because it has been suggested that this parasite may be a factor in the spread of antigen (Barbotin and Qudart, 1972).

The overwhelming majority of the people who constitute this reservoir of hepatitis are symptomless. Only a fraction presents with clinical disease and jaundice as is illustrated by three of our cases. It would appear that the incidence of sporadic icteric hepatitis in this country is largely a reflection of widespread antigenemia. It is only the tip of an iceberg. It is interesting to note in this regard that out of three carriers who developed jaundice, two continued to show antigenemia while one became antigen negative after the first week of illness. This patient would have been considered to be suffering from antigen negative hepatitis if his previous condition was not known.

The effects of antigenemia on the development of chronic liver disease and cirrhosis are not brought out by this study. No case of chronic hepatitis or cirrhosis was seen. A possible reason for this may be the young age of our carriers as well as the lack of drug addiction and alcoholism amongst them. It is, however, evident that the liver in a large number of people is being subjected to the destructive action of hepatitis virus. Considering that cases of viral hepatitis and especially anicteric hepatitis do develop cirrhosis (Klatskin, 1958; Cooper et al., 1966; Chung et al., 1964) this enormous unsuspected pool of hepatitis and widespread antigenemia would conceivably contribute towards the development of cirrhosis.

It should be conceded that this hypothesis, although attractive, is merely a speculation at this stage. Only by following a sufficient number of cases over a period of time, one could hope to answer this question.

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