Viral hepatitis and hepatitis B antigen: recent advances

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Summary

Recent advances in hepatitis research have shed new light on the etiology, pathogenesis, epidemiology and prevention of type B hepatitis infection. The so-called 'Dane' particle is probably the complete hepatitis B virion; its outer coat is the hepatitis B (Australia) antigen (HB Ag) and its inner core is an immunologically distinct particle. Subtypes of HB Ag (a, d, y, w and r) are useful indices for epidemiological surveys. Concepts of epidemiology have changed: type B hepatitis is transmissible by contact as well as by inoculation. The presence of HB Ag in blood is indicative of the presence of hepatitis B virus. Tests to detect antigen and use of voluntary blood donors have played a major role in the decreased incidence of post transfusion hepatitis. A special hepatitis B gammaglobulin preparation and a heat-inactivated hepatitis B vaccine have proved to be effective in preliminary studies.

THE term viral hepatitis refers to two immunologically distinct entities: type A (infectious) hepatitis and type B (serum) hepatitis. Viral hepatitis, type A is an ancient disease which was described by Hippocrates as an 'infectious icterus' more than 2000 years ago. In contrast, type B hepatitis has a more recent history since the first outbreak was recognized in 1883, less than 100 years ago (Lürman, 1885).

Evidence for the viral etiology of hepatitis stems in great part from investigations by MacCallum and Bradley in the United Kingdom (1944), Havens *et al.* (1944), Paul *et al.* (1945), and Neeffe *et al.* (1945) in the United States in the early 1940s. They identified the two immunologically distinct types of hepatitis which were designated type A and type B. These observations were extended by Murray *et al.* (1955) in the early 1950s and by our group in the late 1950s and 1960s (Ward *et al.*, 1958; Krugman *et al.*, 1959, 1962, 1967).

Our studies were conducted in a large institution for mentally retarded residents where hepatitis was highly endemic. During the course of these studies we had an opportunity to observe patients with hepatitis from the time of exposure, during the incubation period, after onset of jaundice or abnormal serum transaminase activity, and for many years

thereafter. The serial samples of serum which were obtained provided valuable materials for the characterization of the clinical, epidemiological and immunological aspects of the infection. The background of this investigation is described in detail in previous publications (Krugman *et al.*, 1959, 1962, 1967, 1970).

In the mid 1960s it became obvious that two types of hepatitis were endemic in the institution. One type, designated MS-1, resembled typical viral hepatitis, type A; it had a relatively short incubation period. The other type, MS-2, was associated with a longer incubation period and it resembled viral hepatitis, type B. It was observed that in this long incubation period, hepatitis infection was transmissible by mouth and by contact as well as by inoculation. The differential features of MS-1 and MS-2 types of hepatitis are shown in Fig. 1 and Table 1.

The discovery of Australia antigen (Blumberg *et al.*, 1965) and its association with hepatitis B virus infection (Prince, 1968; Krugman *et al.*, 1970) provided the technology needed to further clarify the natural history of hepatitis. During a seminar on viral hepatitis in Paris in 1971, Dr John F. Enders highlighted this important development when he said: 'After a long and arid period, a new and exhilarating phase in the study of hepatitis has begun. The discovery of Australia antigen came like an unexpected shower on desert soil'.

In a recent report, a WHO Scientific group (1973) proposed that Australia antigen be referred to as hepatitis B antigen (HB Ag) and the corresponding antibody as hepatitis B antibody (HB Ab). This recommendation was based on the evidence that the antigen had a specific association with hepatitis B virus. Therefore, the term 'Australia' could be misleading because of the implication of an association with that country. The term hepatitis-associated antigen (HAA) was used before the specificity of the antigen for type B hepatitis was proved.

Hepatitis B antigen

The nature of HB Ag has been described in detail in several excellent reviews by Professor Zuckerman

FIG. 1. Serum glutamic oxaloacetic transaminase (SGOT) and thymol turbidity (TT) response following exposure to hepatitis A virus (MS-1 strain) and hepatitis B virus (MS-2 strain). Jaundice when present is observed at time of peak SGOT level. —, SGOT; ---, TT.

Table 1. Viral hepatitis, types A and B: Clinical epidemiological and immunological features compared

	Type A	Type B
Incubation period	15-40 days	50-180 days
Type of onset	Usually acute	Usually insidious
Fever	Common—precedes jaundice	Less common
Age group affected	Usually children and young adults	All age groups
Jaundice	Rare in children; more common in adults	Rare in children; more common in adults
Abnormal SGOT	Transient—1-3 weeks	More prolonged—1-8+ months
Thymol turbidity	Usually increased	Usually normal
IgM levels	Usually increased	Usually normal
HB Ag (Australia antigen in blood)	Not present	Present in incubation period and acute phase; occasionally may persist
Virus in faeces	Present during late incubation period and acute phase	Probably present but no direct proof
Virus in blood	Present during late incubation period and early acute phase	Present during late incubation period and acute phase; occasionally present for months and years
Immunity		
Homologous	Present	Present
Heterologous	None	None

(1971, 1972), a participant at this meeting. Briefly, it is a lipoprotein, immunologically distinct from beta lipoproteins. Electronmicroscopic examination of serum containing the antigen has revealed evidence of the following types of virus-like particles: (1) spherical particles, 20 nm in diameter; (2) elongated particles, 100 or more nm long and 20 nm in diameter; and (3) the so-called 'Dane particles' which are 42 nm in diameter, consisting of an outer coat and an inner core (Dane, Cameron and Briggs, 1970).

It has been postulated that the 'Dane particle' is the complete hepatitis B virion and the smaller 20 nm particles represent excess virus-coat material or incomplete particles.

Subspecificities of HB Ag have been described by LeBouvier (1971, 1972). He and other workers have observed a common group specificity for the antigen which has been designated 'a', and two mutually exclusive subspecificities, 'd' and 'y'. Two additional determinants, 'w' and 'r' were described by Bancroft,

Mundon and Russell (1972). The 'd' and 'y' determinants reflect the genotype of HB Ag and therefore they are useful indices in epidemiological surveys.

Studies of the inner component of the 42 nm particle by Almeida, Rubenstein and Stott (1971) are being extended by other investigators who are attempting to characterize the biophysical and antigenic composition of the core. Their findings should further define the features of the etiologic agent of viral hepatitis, type B.

Epidemiological aspects of type B hepatitis

Until recent years it was assumed that hepatitis B virus (HBV) was transmissible exclusively by parenteral inoculation. However, concepts of the epidemiology of viral hepatitis, type B have changed significantly since 1967. It is now clear that non-parenteral transmission of HBV plays an important role in the spread of the disease.

Healthy chronic carriers and patients with acute or chronic hepatitis are the chief sources of the virus. The infection is transmitted to susceptible persons by transfusion of contaminated blood, blood-products, needles and syringes. Accidental inoculation or ingestion of infectious materials may occur in health workers. In areas of the world where primitive sanitary conditions exist, the infection is spread by contact.

Seroepidemiological surveys for the presence of HB Ag and HB Ab have confirmed the existence of the disease in all parts of the world. The disease is most prevalent among populations living under conditions of poor sanitation and crowding.

The period of infectivity of patients with viral hepatitis, type B is variable; it is dependent upon the presence or absence of a chronic carrier state.

Hepatitis B antigen may be detected in the blood 2 weeks to 2 months before onset of hepatitis. In most patients the antigen is no longer detectable from several days before to about 3 months after onset of jaundice.

The detection of HB Ag in blood is indicative of the presence of infectious HBV. However, tests for HB Ag may not be sensitive enough to detect small amounts of antigen which may be present in blood containing HBV. Therefore, a negative test for HB Ag does not rule out the presence of virus. Under these circumstances HB Ag-negative blood could cause viral hepatitis, type B.

Clinical aspects of viral hepatitis

Prospective observations of the clinical course of viral hepatitis have revealed differences between type A and type B infection. As indicated in Fig. 1 and Table 1, type A infection is characterized by a shorter incubation period and a shorter duration of abnormal serum transaminase activity. Our prospective studies have revealed that HB Ag is not present in the serum of patients with viral hepatitis, type A; it is consistently detected some time during the course of viral hepatitis, type B. The antigen was not detected in serial samples of serum obtained from forty patients with type A hepatitis. In contrast, HB Ag was detected in forty-nine of fifty patients with type B hepatitis.

The serum specimens from the one patient who had no detectable HB Ag by immunodiffusion and complement fixation were retested for antigen by radioimmunoassay. This more sensitive test revealed the presence of HB Ag in a specimen obtained several days before the SGOT became abnormal.

The variable course of hepatitis B virus infection

FIG. 2. Serial observations of fourteen patients with icteric viral hepatitis, type B. Stippled areas indicate HB-Ag detectable in blood. Black bars indicate presence of jaundice. Duration of antigenaemia in patients no. 1-13 ranged between 1 day and 127 days.

FIG. 3. Serial observations of twenty-five patients with anicteric viral hepatitis, type B. Stippled areas indicate HB Ag detectable in blood. Note high incidence of chronic carrier state.

is illustrated in Figs. 2 and 3. As indicated in Fig. 2, the carrier state was rarely observed in patients with icteric hepatitis B virus infection. Of fourteen patients followed prospectively only one was a carrier. Serial observations of the remaining thirteen patients revealed that HB Ag was detectable for an average of 54 days; the range was 1–127 days. Antigen was consistently detected before onset of jaundice. Occasionally HB Ag became non-detectable before onset of jaundice (patients no. 1 and 2 in Fig. 2). In general, HB Ag persisted for several days or weeks after subsidence of jaundice (patients no. 4, 8, 10, 11, 12 and 13, Fig. 3). However, in some instances the jaundice persisted longer than the antigen (patients no. 3, 5, 7 and 9, Fig. 2).

The association of the chronic carrier state with anicteric hepatitis B virus infection is shown in Fig. 3. More than half of this group of twenty-five patients became chronic carriers. The persistence of HB Ag in ten patients who were not carriers ranged between 13 and 139 days, average 73 days.

During a meeting of the American Pediatric Society in May of this year, Dr Gerety and his colleagues reported the results of tests for HB Ag in three groups of children: (1) normal U.S. children with no known exposure to hepatitis; (2) children from West Africa and two Pacific islands where hepatitis was highly endemic; and (3) children from institutions where hepatitis was endemic. An extraordinarily high incidence of chronic carriers was observed among children who lived in endemic areas.

Hepatitis B antigen and post-transfusion hepatitis

When it became apparent that the detection of

HB Ag was indicative of the presence of hepatitis B virus, the routine testing of donor blood was instituted. Since 1970 many millions of units of blood have been screened for HB Ag. Great variations in the prevalence of HB Ag in presumably healthy blood donors have been found in different parts of the world. The prevalence of the antigen has been shown to be related to such factors as socioeconomic status and whether the blood is obtained from a volunteer or paid donor.

The overall incidence of HB Ag in volunteer blood donors in the United States is 0.15% (Szmuness *et al.*, 1973). Regional variations have been observed, the lowest incidence being in the North Central States (0.06%) and the highest in the South-eastern States (0.17%) and Puerto Rico (0.34%). In contrast with these observations, the incidence of HB Ag-positive blood obtained from paid commercial donors was approximately ten times higher (Cherubin and Prince, 1971).

The high incidence of HB Ag in blood obtained from paid donors confirmed past experience indicating that the use of blood from this source was associated with a high incidence of post-transfusion hepatitis. These findings provided an added stimulus to increase the voluntary donations of blood. A prospective study by Alter *et al.* (1972) revealed the effectiveness of excluding both commercial and HB Ag-positive donors. They demonstrated that the overall frequency of hepatitis was reduced from 33% (20 cases per 1000 units) in a study conducted between 1967 and 1969, to 7.1% (3.7 cases per 1000 units) in a more recent study in 1970 and 1971. An 82% decrease in the hepatitis rate was achieved. In

the first study many patients received commercial blood at a time when HB Ag testing was not done. In the second study both commercial donors and HB Ag-positive donors were excluded. Alter *et al.* (1972) have estimated that the substitution of HB Ag-negative for HB Ag-positive blood while continuing the use of commercial blood would have decreased the 33% rate of hepatitis to 25%, a reduction of 25%. The exclusion of commercial donors, however, would have decreased the rate from 33% to 10%, a reduction of 70%.

Studies by various investigators are currently in progress to determine the effect of the presence of hepatitis B antibody in donor blood. Such antibody was found in 10–40% of adults when sensitive techniques were employed for its detection. Preliminary reports by Gocke and Panick (1972) and by Caggiano (1972) indicated that the transfusion of HB Ab-positive blood was not associated with an increased risk of post-transfusion hepatitis.

To date, the routine screening of blood for the presence of HB Ag has played an important role in the control of post-transfusion hepatitis. The testing of blood has had a direct effect by identifying potentially infectious units of blood. The indirect effect has been more important because the results of the test have confirmed the increased risk of using blood from commercial donors. The limitations of the test for HB Ag have been twofold: (1) lack of sensitivity to detect all infectious units of blood; and (2) identification of only one of various causes of post-transfusion hepatitis; others include hepatitis A virus, cytomegalovirus and EB (Epstein-Barr) virus.

The advent of more sensitive tests for the detection of HB Ag should have a beneficial, though not highly significant effect on the incidence of post-transfusion hepatitis. Since most healthy carriers have a relatively high titre of circulating HB Ag, only a small number of additional carriers will be discovered by the use of radioimmunoassay and other highly sensitive tests. Further reduction in the incidence of post-transfusion hepatitis will require the development of a biological test for the detection of hepatitis B virus. The ultimate control of viral hepatitis types A and B will depend in great part on the development of effective active and passive immunization procedures.

Prospects for prevention of viral hepatitis, types A and B

Passive immunization

Viral hepatitis, type A. The efficacy of standard immune serum globulin for the prevention or modification of type A hepatitis has been well documented. The results of controlled studies by many investigators during the past 30 years have confirmed the

value of this passive protection when the gamma globulin is given shortly after exposure to a known contact.

Viral hepatitis, type B. The efficacy of standard immune serum globulin for the prevention of type B hepatitis has been a controversial subject for many years. Reports of its value have varied from limited protection to none at all. This phenomenon is due in part to the fact that most lots of standard gammaglobulin have non-detectable or low levels of HB Ab.

The preparation of specific hepatitis B immune serum globulin from plasma containing high levels of HB Ab provided a preparation with an antibody titre which was 25,000–50,000 times higher than the standard licensed product (Prince *et al.*, 1971). The preliminary trials reported by our group (Krugman *et al.*, 1971) and by Soulier *et al.* (1972) revealed that the use of this specific globulin was associated with a protective effect, an attenuated infection, when present, and a decreased chronic carrier rate. At the present time the National Institutes of Health and the Veterans Administration are conducting a nationwide trial to evaluate the efficacy of this special gammaglobulin preparation. It is anticipated that the results of these studies will be available by 1975.

Active immunization

Viral hepatitis, type A. Failure to cultivate hepatitis A virus or to identify an antigen associated with it has retarded the development of an active immunizing agent. However, the confirmatory reports of the successful propagation of hepatitis A virus in marmoset monkeys are encouraging.

FIG. 4. Course of hepatitis B virus infection (MS-2 strain) in twenty-five unimmunized children after a parenteral exposure to MS-2 serum. Black dots, HB Ag; vertical lines, SGOT abnormal; shaded area, anti-HB Ag; black bars, jaundice.

FIG. 5. Active immunization with heat-inactivated MS-2 serum. Note (1) protective effect; (2) evidence of an attenuated infection; and (3) a decreased chronic carrier rate in these immunized children when compared with the unimmunized group (Fig. 4). Black dots, HB Ag; vertical lines, SGOT abnormal; shaded area, anti-HB Ag; black bars, jaundice.

Viral hepatitis, type B. The development and use of active immunizing procedures have been reported by our group (Krugman *et al.*, 1971a, b) and Soulier *et al.* (1972). Serum containing our MS-2 strain of HBV was diluted in distilled water and heated for 1 min at 98° C. The heat-treated serum proved to be antigenic and non-infectious. The results of active immunization of twenty-nine children were summarized in a recent report (Krugman *et al.*, 1973). The data are shown in Figs. 4 and 5.

As indicated in Fig. 4 a parenteral inoculation of unheated MS-2 serum was followed by antigenemia in all twenty-five unimmunized children; abnormal SGOT values were observed in twenty-four members of this group. In contrast, of twenty-nine children who received one to three inoculations of heat-inactivated MS-2 serum, 4–8 months before a parenteral exposure to unheated MS-2 serum, nineteen (65%) were protected (Fig. 5). The use of this active immunizing procedure was associated with a protective effect, a more attenuated hepatitis B virus infection and a decreased HB Ag chronic carrier rate.

The further development of a hepatitis B vaccine will be accelerated by the availability of a suitable animal model and a sensitive tissue culture assay. It is encouraging that typical HBV infection has been successfully propagated in susceptible chimpanzees (Barker *et al.*, 1973). A sensitive tissue culture assay is not available as yet. Unlike hepatitis B immune serum globulin which should be available by 1975, it is difficult to forecast the probable date for the

availability of a safe and effective hepatitis B vaccine. It is hoped that this objective will be achieved before the end of the 1970s.

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Discussion

In answer to the question from Professor Daniel Alagille of Paris, Professor Krugman stated that he had no experience in using specific immunoglobulin with a high concentration of antibody to hepatitis B antigen to treat hepatitis B infection. Just as gamma-globulin is worthless in measles once the disease is established, it is unlikely to influence hepatitis. Controlled trials are, however, in progress in the USA to compare the role of hyperimmune gammaglobulin with standard gammaglobulin in fulminant hepatitis. Gammaglobulin given within 4 hr of test inoculation of hepatitis B antigen-containing serum, was protective, antibody appeared in the serum within 3 hr. It might be possible to give such antibody for

up to 1 week after inoculation and still be protected from antigenaemia. There was good reason for thinking that hyperimmune gammaglobulin would be protective for 'needle prick' exposure but larger volumes of hepatitis B antigen in blood may be a greater challenge.

Dr B. Gans, Lewisham, enquired what happened when patients were exposed to both hepatitis A and hepatitis B. Professor Krugman replied that the original serum pool had in fact contained both A and B and in most instances, infection occurred in response to hepatitis A only; occasionally, however, hepatitis A infection was followed 1–2 months later by hepatitis B infection.