Viral Hepatitis, Type B

LEWELLYS F. BARKER

Division of Blood and Blood Products, Bureau of Biologics, Food and Drug Administration, Bethesda, Maryland 20014

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INTRODUCTION

Hepatitis B virus (HBV) is a DNA virus which is highly host and organ specific; to date it has only been found to infect hepatocytes of man and of a few nonhuman primate species. Despite the continuing failure of virologists to find an in vitro system for propagating HBV, it has been possible to gain a great deal of information about the agent and about viral hepatitis, type B, as a result of the discovery of the Australia antigen, now termed hepatitis B surface antigen (HB,Ag), and the recognition of its significance (1–4). The presumptive infectious form of HBV is a 40–42-nm particle, known as the Dane particle (5), which consists of an inner nucleocapsid core, termed hepatitis B core antigen (HB,Ag) (6), and an outer lipoprotein coat composed of HB,Ag. The respective antibodies for the inner and outer components of HBV are called anti-HB, and anti-HB, respectively. In the last several years a number of tests have been developed for detecting these antigens and antibodies (7). The most sensitive methods are radioimmunoassays (RIA), which use solid phase or double antibody techniques for separating specifically bound from free radiolabeled proteins. Almost as sensitive and avoiding the requirements for working with radioactive isotopes are the following hemagglutination techniques: passive hemagglutination (PHA) for anti-HB, detection, reversed passive hemagglutination (RPHA) for HB,Ag detection, and immune adherence hemagglutination (IAHA) for anti-HB, detection. A number of less sensitive methods, including agar gel diffusion, counterimmunoelectrophoresis, complement fixation, and reversed passive latex agglutination, are valuable for certain specific applications, but the more sensitive methods have vastly increased our understanding of the clinical disease, epidemiology, and approaches to prevention of type B hepatitis.

CLINICAL FEATURES

Acute HBV infection can produce a broad spectrum of clinical manifestations, ranging from no overt disease to fulminant fatal hepatitis. The interval between exposure and appearance of detectable serum HB,Ag is related to the infectivity titer of the inoculum (8,9) and probably also to the route of exposure; it may be as short as 2 or 3 weeks with very high titer inocula and as long as 3 or 4 months with low titer inocula. Elevated serum enzymes, icterus, and other clinical signs as well as symptoms tend to appear some days or weeks after the initial appearance of HB,Ag; they often appear in close proximity to peak HB,Ag levels (2,3,10). In most cases, anti-HB, activity appears during the acute illness, while HB,Ag is still present (11). The majority of infected people develop anti-HB, after HB,Ag clearance and during

1Address correspondence to: Lewellys F. Barker, M.D., Bureau of Biologics, FDA, 8800 Rockville Pike, Bethesda, Md. 20014.
convalescence, although appearance of this antibody may be delayed for a number of weeks or months after HB,Ag disappearance (12,13). A small minority of individuals infected with HBV do not develop detectable levels of HB,Ag, anti-HB, or anti-HB, during the acute illness or in convalescence.

The HBV carrier state, manifested by persistence of HB,Ag and anti-HB, and absence of detectable anti-HB, develops in a proportion of infected individuals, estimated to be 5–10% of adults infected in the United States. The carrier state may last from a few years to the lifetime of the individual. Host-related factors which appear to predispose to the development of the carrier state include infection at an early age, mild or anicteric disease, and a depressed immune response because of underlying disease or immunosuppressive treatment (14–19).

Observation of factors which predispose people infected with HBV to become carriers has led to considerable speculation regarding the role of humoral and cell-mediated immune responses in the pathogenesis of type B hepatitis. Circulating HB,Ag/anti-HB, complexes have been suggested as causative factors in fulminant hepatitis and also in some of the extrahepatic manifestations of type B hepatitis, including arthritis, urticaria, polyarteritis, and glomerulonephritis (20). Cell-mediated immunity has been considered a possible mediator of hepatocellular damage in acute and chronic hepatitis, and deficient cell-mediated immunity with consequent deficient antibody production has been postulated as the underlying defect responsible for the development of the carrier state (21). Direct proof of these hypotheses is difficult to obtain because laboratory methods for detecting cell-mediated immunity are not as well standardized and quantitative as tests for humoral immune responses. Consequently there is considerable variation in the results and interpretation of tests of the cellular immune response in patients with type B hepatitis. Nevertheless, it is likely that a better understanding of the nature and significance of cellular immune response to HBV infection is needed to understand why some people become carriers and also why there are such variegated clinical manifestations of acute infections as well as of the carrier state. In individuals with chronic HBV infections, it is possible to have essentially no detectable liver disease or to have complications of increasing severity, from chronic persistent hepatitis to chronic active hepatitis, macronodular cirrhosis, and primary hepatocellular carcinoma.

There are two additional markers of HBV infection which are thought to correlate with the amount of infectivity in serum. The first of these is the HBV-specific DNA polymerase, described by Hirschman and by Robinson and their colleagues (22,23), and the second is the e antigen described by Magnus and Espmark (24). Both of these markers are present in sera containing large numbers of Dane particles, and therefore they may well be indicators of high levels of infectivity. The nature and source of the e antigen have not been fully clarified, but it is clear that neither detectable DNA polymerase which is closely associated with HB,Ag nor detectable e antigen is a prerequisite for infectivity for serum. Evidence has been cited in support of the hypothesis that anti-e in HB,Ag carriers’ sera is indicative of lack of infectivity of these sera, but it seems premature to judge the reliability of this marker. However, particularly in the case of e and anti-e, it may be necessary to develop more sensitive detection methods, as was the case for HB,Ag and anti-HB, in order to develop a clearer picture of the prevalence and significance of these serologic markers.
EPIDEMIOLOGY

Extremely important and sometimes surprising insights into the epidemiology of type B hepatitis have resulted from the application of tests for hepatitis B antigens and antibodies. It is clear, for example, that therapeutic transfusion or injection of blood and blood products contaminated with HBV is a relatively uncommon mode of transmission of type B hepatitis. The early population studies by Blumberg and his associates established that HBsAg prevalence is much higher in developing countries in tropical areas where therapeutic blood transfusion is uncommon than in the United States and other western countries where treatment with blood and blood products is much more widely practiced (25).

Probably the commonest modes of spread of type B hepatitis are from infected mothers to infants and by members of families by close personal contact. Although infants appear to be at highest risk when the mother experiences an acute episode of type B hepatitis during the latter part of pregnancy, there is also ample evidence of infection of infants whose mothers are HBsAg carriers (14). As mentioned above, infection early in life appears to be associated with an extremely high risk of developing chronic infection.

Person-to-person spread by close contact would appear to account for the high prevalence of HBV infection in settings such as custodial institutions for mentally retarded patients as well as in families where one member is a carrier (15,26). Although several studies have provided persuasive evidence that type B hepatitis can be a sexually transmitted disease, the increased risk in families applies to parents, siblings, and offspring as well as spouses (26–28). In view of these documented patterns of person-to-person spread of HBV, it is probably significant that HBsAg has been detected in a number of body fluids other than blood, including urine, saliva, tears, sweat, breast milk, and semen (27). The possible role of these body fluids in spread of the disease and also the possibility that bloodsucking arthropods may serve the same function as contaminated needles have been suggested but not yet definitively established.

Further insights into the epidemiology of type B hepatitis have been provided by the identification of four major subtypes of HBsAg, termed adw, ayw, adr, and ayr (29,30). Subdeterminants of the major subtypes and additional specificities are still being discovered (31). Although there are no definite correlations between infecting subtypes and clinical features of type B hepatitis such as severity, tendency toward chronicity, or manifestations of chronic infections, the subtypes have proved most useful as epidemiologic markers (32–34). In the United States and Western Europe, the adw subtype is found in the majority of carriers and the ayw subtype in most of the remainder, whereas in the Soviet Union and parts of Africa the ayw subtype is predominant (31). The adr subtype is largely concentrated in Southeast Asia, and the ayr subtype is relatively rare, only a few examples having been identified to date. It is firmly established that the subtypes are virus-determined specificities which breed true in infected people and experimental animals (9,34). There are also a number of examples of individuals simultaneously infected with the adw and ayw subtypes who produce HBsAg with adyw specificity (32).

IMPACT OF TESTING ON TRANSFUSION THERAPY

Testing for the presence of HBsAg in blood collected for transfusion or for further manufacturing into plasma derivatives has become a standard procedure in many
countries over the past 5 years. Since September 1975, blood banks in this country have been required to test every unit collected by one of the highly sensitive, third-generation methods (RIA or RPHA).

Since the interval between transfusion and onset of type B hepatitis may be many months and HBV infections are often subclinical, the best means of studying the impact of testing on blood safety is to follow transfused patients prospectively. Such prospective studies provided the first unequivocal evidence of the validity of HBsAg as a marker for the presence of HBV, in that virtually all susceptible individuals who received units of blood containing HBsAg developed some evidence of exposure to HBV (2,35–37). Over half the recipients of blood containing HBsAg developed enzyme changes indicative of liver damage, but a lower proportion developed overt clinical disease. Much lower rates of enzyme elevations and clinical disease were seen in control groups of patients who were transfused with blood that was nonreactive for HBsAg. In recent prospective studies of patients transfused with blood which has been tested and found nonreactive by one of the most sensitive available techniques (RIA), there is a small residue of HBV infections, presumably from units of blood contaminated with HBV but containing too little HBsAg for detection by present methods (38,39).

In addition to the direct benefits of avoiding transfusion of units of HBsAg-reactive blood, testing has had a very significant indirect benefit by providing quantitative indications of the excessively high hepatitis risk associated with blood collected from paid donors by commercial blood banks (37,40). Earlier studies, prior to the application of tests for HBsAg, provided considerable evidence of a higher risk of hepatitis in recipients of blood from paid donors as compared with blood from voluntary donors (41). Prospective studies since the advent of HBsAg testing showed that a greater effect on the safety of transfused blood would be realized by elimination of blood from paid donors than by testing alone (42,43), and accordingly the American Blood Commission established a goal of an all-voluntary donor system by the end of 1975. Further effort to achieve this goal has been stimulated by an FDA proposed requirement that all units of blood be labeled to indicate whether they were collected from voluntary or paid donors and, in the latter case, to indicate that blood from paid donors carries an increased risk of transmitting viral hepatitis (44). Blood from paid donors not only carries an increased risk of contamination with HBV but also has been found to be associated with a markedly increased incidence of non-A, non-B hepatitis (38,42,43,45).

Anti-HBs in donor blood does not appear to be associated with an increased risk of infectivity. In fact, anti-HBs appears to be a better indicator of active HBV replication than anti-HBc, and therefore anti-HBs is currently being evaluated as a marker for identifying infectious units of blood which do not contain detectable HBsAg (46).

Transmission of type B hepatitis by certain plasma derivatives, which are made from pooled plasma collected by plasmapheresis, remains a serious problem, which is not likely to be resolved by third-generation testing (47). The highest risk plasma derivatives are antihemophilic factor concentrates for treatment of hemophilia A, factor II, VII, IX, and X concentrates for treatment of hemophilia B, and fibrinogen, for which there appear to be few valid clinical indications. A particularly serious problem has been the promiscuous use of factor II, VII, IX, and X concentrates as broad-spectrum hemostatic agents in postoperative patients and patients with liver disease. The result has been a number of clusters of type B hepatitis cases with considerable morbidity and mortality (48,49). Experimental efforts are in progress to
free these products of HBV by introduction of steps to remove or inactivate the virus, but these efforts have met with only limited success to date. HBV removal from red blood cells by washing, with or without a freeze–thaw cycle, is also being evaluated as a means of improving the safety of red cell transfusions. Although washing procedures will clearly reduce the amount of contamination of red blood cells with HBV, it seems unlikely that complete removal of the virus will be accomplished by this approach.

PROGRESS TOWARDS CONTROL: PASSIVE AND ACTIVE IMMUNIZATION

Initial pilot studies of prevention of type B hepatitis with high titer hepatitis B immune globulin (HBIG) gave promising results of partial effectiveness (50,51). Accordingly, a number of controlled clinical studies were undertaken in this country and abroad (28,52–56). In all of these studies individuals at high risk of acquiring type B hepatitis due to accidental inoculation, being on the staff or being a patient in renal dialysis units or being exposed by close contact to a spouse with acute type B hepatitis received either HBIG or an immune serum globulin preparation with a low level of anti-HB. Preliminary reports of these studies have revealed partial and temporary protection.

Development of experimental hepatitis B vaccines is in a much earlier phase of evaluation in experimental animals using the chimpanzee model. Two groups in this country have independently prepared experimental vaccines consisting of formalin-treated HBAg purified from human plasma. Preliminary reports of inoculation of these preparations into susceptible chimpanzees have revealed no residual infectious virus and definite protection against challenge with HBV (57, 58). Although it will unquestionably require a great deal of painstaking effort over a number of years to evaluate the safety and effectiveness of experimental hepatitis B vaccines, the partial effectiveness, at best, of passive immunization and the fact that the disease cannot be controlled by HBAg testing alone make vaccine development an endeavor that deserves high priority in our national biomedical research and development activities.

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