Hepatitis B Virus And Blood Transfusion Safety In Sub-Saharan Africa

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Citation

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Abstract

Hepatitis B virus (HBV) is the most common cause of serious liver infection in the world. It is estimated that worldwide more than two billion people have been infected by HBV and 350 million people have chronic infection. The HBV is highly contagious and transmission of HBV occurs via percutaneous or permucosal routes, and infective blood or body fluids can be introduced at birth, through sexual contact or by contaminated needles. Transfusion-transmitted HBV infection is increasingly becoming a major mode of transmission of HBV in the high-prevalence areas in sub-Saharan Africa. There is a high level of occurrence of blood demanding health conditions in many parts of sub-Saharan Africa. Due to endemicity of infections causing anemia, malnutrition, and surgical and obstetrical emergencies associated with blood loss in the sub-Saharan Africa, the demand for blood transfusion services is high and increase the possibility of the transmission of HBV (and other blood-borne pathogens) through contaminated blood. Blood safety remains an issue of major concern in transfusion medicine in this part of the globe because national blood transfusion services and policies, appropriate infrastructure, trained personnel and financial resources are inadequate. As part of public health interventional measures, the transmission of HBV can be minimized by the screening of donors prior to donation, exclusion of high-risk donors, followed by the in-vitro screening of donations for HBsAg prior to transfusion. Accurate assessment of transfusion-transmitted HBV infection which necessitates knowledge about donation histories and person-years at risk is very essential in order to establish comprehensive frameworks for monitoring blood donations and infectious disease markers which remains a key to monitoring blood safety.

INTRODUCTION

Hepatitis B virus (HBV) is the most common cause of serious liver infection in the world. It is estimated that worldwide more than two billion people have been infected by HBV and 350 million people have chronic infection [1]. The virus causes transient and chronic infections of the liver. Transient infections may produce serious illness, and approximately 0.5% terminates with fatal, fulminant hepatitis while chronic infections may also have serious consequences: nearly 25% terminate in untreatable liver cancer [2]. Worldwide deaths from liver cancer caused by HBV infection probably exceed one million per year [34]. The clinical presentation Hepatitis B ranges from subclinical hepatitis to symptomatic hepatitis and, in rare instances, fulminant hepatitis [5]. Long-term complications of hepatitis B include cirrhosis and hepatocellular carcinoma [6]. Hepatitis B infection has thus assumed an important public health problem due to its chronic serious sequelae. It has been estimated that at the most, 33% of the infected subjects have evidence of clinical hepatitis [7], and depending on the age of infection, up to one third of infected patients become chronic carriers of hepatitis B surface antigen (HBs Ag) [7]. Chronic carriers have a higher incidence of and mortality due to hepatocellular carcinoma and cirrhosis [8]. Perinatal or childhood infection is associated with few or no symptoms, but it has a high risk of becoming chronic [5].

Persons with chronic HBV infection are predisposed to chronic liver disease and have a greater than 200-fold increased risk of hepatocellular carcinoma [9]. Fulminant hepatic failure occurs in approximately 0.1-0.5% of patients and is believed to be caused by massive immune-mediated lysis of infected hepatocytes. Various extrahepatic manifestations, including urticarial rashes, arthralgia, and arthritis, are associated with acute clinical and subclinical HBV infection, as well as multiple immune-complex disorders such as Gianotti-Crosti syndrome (papular acrodermatitis), necrotizing vasculitis, and hypocomplementemic glomerulonephritis [910]. HBV is associated with 20% of the cases of membranous nephropathy in children. Essential mixed cryoglobulinemia, pulmonary hemorrhage related to vasculitis, acute

pericarditis, polyserositis, and Henoch-Schönlein purpura have been reported in association with HBV infection [9]. The pathogenesis and clinical manifestations are due to the interaction of the virus and the host immune system. The latter attacks the HBV and causes liver injury. Activated CD4+ and CD8+ lymphocytes recognize various HBV-derived peptides located on the surface of the hepatocytes, and an immunologic reaction occurs. Impaired immune reactions (eg, cytokine release, antibody production) or relatively tolerant immune status results in chronic hepatitis [10]. In particular, a restricted T cell–mediated lymphocytic response occurs against the HBV-infected hepatocytes. The final state of the disease is cirrhosis. Patients with cirrhosis and HBV infection are likely to develop hepatocellular carcinoma [610].

BIOLOGY HEPATITIS B VIRUS

The HBV is a Hepadna-virus. It is an extremely resistant strain capable of withstanding extreme temperatures and humidity and can survive when stored for 15 years at -20°C, for 24 months at -80°C, for 6 months at room temperatures, and for 7 days at 44°C [9]. The viral genome consists of a partially double-stranded circular DNA of 3.2 kilobase pairs that encodes 4 overlapping open reading frames including the surface or envelope gene encoding the pre-surface 1, pre-surface 2, and the surface protein. The core gene, encoding for the core nucleocapsid protein and the e antigen, the X gene encoding the X protein and polymerase gene encoding a large protein promoting priming, RNA-dependent and DNA-dependent DNA polymerase and RNase H activities [911]. The structure of this virion is a 42-nm spherical double-shelled particle consisting of small spheres and rods, with an average width of 22 nm. The mechanism of RNA-directed DNA synthesis has been well characterized through genetic as well as biochemical studies [1213]. In contrast, early events of the viral life cycle, including entry, uncoating, and delivery of the viral genome into the cell nucleus, are not well understood and this is, in part, due to the absence of cell lines that are susceptible to hepadnavirus infection [11].

HBV displays a wide genetic diversity. Although HBV is a DNA virus, it has several unique features that result in a much higher mutation rate than usually observed for DNA viruses [14]. HBV replicates via an RNA intermediate that is synthesized by reverse transcriptase activity of the viral polymerase. Reverse transcriptase does not correct

transcription errors, leading to a higher mutation rate during replication than generally observed for DNA viruses. The high rate of hepatitis B virus production (as high as 10^{13} virions per day) allows the virus to generate theoretically every possible single mutation in the genome every day. In addition, the compact organization of the HBV genome, with its overlapping reading frames, allows almost every mutation to have potentially pleiotropic effects [14]. There are 5 mainly antigenic determinants: a, common to all HBsAg and d, y, w, and r, which are epidemiologically important. The core antigen, HBcAg, is the protein that encloses the viral DNA. It also can be expressed on the surface of the hepatocytes, initiating a cellular immune response. The e antigen, HBeAg, comes from the core gene and is a marker of active viral replication. Usually, HBeAg can be detected in patients with circulating serum HBV DNA [9].

NATURAL HISTORY HEPATITIS B VIRUS INFECTION

HBV is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma worldwide [15]. The most serious consequences of HBV infection are primarily the result of chronic HBV infection, which occurs in 6%-10% of infected adults, approximately 25% of infected children aged 1 to 5 years, and 70%-90% of infected infants [151617]. Four different stages have been identified in the viral life cycle [91118]. The first stage is immune tolerance. The duration of this stage for healthy adults is approximately 2-4 weeks and represents the incubation period. For newborns, the duration of this period often is decades. Active viral replication is known to continue despite little or no elevation in the aminotransferase levels and no symptoms of illness. In the second stage, an inflammatory reaction with a cytopathic effect occurs. HBeAg can be identified in the sera, and a decline of the levels of HBV DNA is seen. The duration of this stage for patients with acute infection is approximately 3-4 weeks (symptomatic period). For patients with chronic infection, 10 years or more may elapse before cirrhosis develops.

In the third stage, the host can target the infected hepatocytes and the HBV. Viral replication no longer occurs, and HBeAb can be detected. The HBV DNA levels are lower or undetectable, and aminotransferase levels are within the reference range. In this stage, an integration of the viral genome into the host's hepatocyte genome takes place. HBsAg still is present. In the fourth stage, the virus cannot be detected and antibodies to various viral antigens have been produced. Different factors have been postulated to influence the evolution of these stages, including age, sex, immunosuppression, and co-infection with other viruses.

According to Seeger and Mason [9], one of the reasons for chronic HBV infections is that the virus causes chronic, noncytocidal infections of hepatocytes, the principal cell type of the liver. Hepatocytes continuously shed virus into the bloodstream, ensuring that 100% of the hepatocyte population is infected. Also, hepatocytes are normally long-lived, with half-lives estimated at 6 to 12 months or longer. The combination of a long-lived, usually nondividing host cell and a stable virus-host cell interaction virtually ensures the persistence of an infection in the absence of a robust host immune response.

TRANSMISSION OF HEPATITIS B VIRUS

The HBV is highly contagious and relatively easy to transmit from one infected individual to another. According to report by the Centre for Disease Control and Prevention (CDC) [19], transmission of HBV occurs via percutaneous or permucosal routes, and infective blood or body fluids can be introduced at birth, through sexual contact or by contaminated needles. Infection can also occur in settings of continuous close personal contact (such as in households or among persons in institutions for the developmentally disabled), presumably via inapparent or unnoticed contact of infective secretions with skin lesions or mucosal surfaces. Furthermore the report indicated that persons at increased risk of acquiring HBV infection include members of the following groups: a) parenteral drug users, b) heterosexual men and women and homosexual men with multiple partners, c) household contacts and sexual partners of HBV carriers, d) infants born to HBV-infected mothers, e) patients and staff in custodial institutions for the developmentally disabled, f) recipients of certain plasma-derived products (including patients with congenital coagulation defects), g) hemodialysis patients, h) health and public-safety workers who have contact with blood, and i) persons born in areas of high HBV endemicity and their children [19].

The HBV carrier rate variation is 1-20% worldwide and this variation is related to differences in the mode of transmission and age at infection [910]. The prevalence of the disease in different geographical areas has been characterized as low, intermediate and high prevalence areas. The low-prevalence areas (rate of 0.1-2%) include Canada, western Europe, Australia, and New Zealand and in these areas of low prevalence, sexual and percutaneous transmission during adulthood are the main modes of transmission. The intermediate-prevalence areas (rate of 3-5%) include eastern and northern Europe, Japan, the Mediterranean basin, the Middle East, Latin and South America, and central Asia and in these areas of intermediate prevalence, sexual and percutaneous transmission and transmission during delivery are the major routes. The High-prevalence areas (rate of 10-20%) include China, Indonesia, sub-Saharan Africa, the Pacific islands, and Southeast Asia and here, the predominant mode of transmission is perinatal, and the disease is transmitted during early childhood vertically from the mother to the infant [910]. In addition to this, transfusion-transmitted HBV infection is increasingly becoming a major mode of transmission of HBV in the high-prevalence areas particularly in sub-Saharan Africa. There is a high level of occurrence of blood demanding health conditions in many parts of sub-Saharan Africa. The increase in road accidents, pregnancy-related hemorrhage, anaemia due to disease conditions and malnutrition, armed conflicts, and violent events in the sub-region, increase the possibility of the transmission of HBV (and other blood-borne pathogens) through contaminated blood.

HEPATITIS B VIRUS AND BLOOD TRANSFUSION IN SUB-SAHARAN AFRICA

The safety of blood products is one of the major issues in the area of transfusion medicine. Transmission of hepatitis B virus (HBV) infection through donated blood is reportedly very common particularly in the developing world including the sub-Saharan Africa. The prevalence of hepatitis B virus chronic carriage in sub-Saharan Africa ranges between 3% and 22% in blood donors [202122]. Typically, more than 50% of blood donors and blood recipients have had natural exposure to HBV, and the need for hepatitis B surface antigen screening of blood donations has often been considered of secondary importance because many donors are not infectious and many recipients are not susceptible [21]. At present, the World Health Organization (WHO) estimates that no more than 50% of the blood supply in sub-Saharan Africa is screened for HBsAg and this low rate of screening is due to lack of perceived utility, lack of funds, or both [23]. Furthermore, no systematic study of donor and recipient populations has been undertaken that could provide the basic data to estimate the transfusion-related risk of HBV infection in high-prevalence areas of Africa.

Due to endemicity of infections causing anemia, malnutrition, and surgical and obstetrical emergencies associated with blood loss in the sub-Saharan Africa, the demand for blood transfusion services is high. However, blood safety remains an issue of major concern in transfusion medicine in this part of the globe because national blood transfusion services and policies, appropriate

infrastructure, trained personnel and financial resources are inadequate. This is aggravated by the pre-dominance of family and replacement, rather than regular benevolent, non-remunerated donors and lack of comprehensive and systematic screening of donated blood for transfusion-transmissible agents other than HIV [24252627282930]. A large number of blood transfusion centers in sub-Saharan Africa, screen donor blood for HIV alone. Other main transfusion transmissible infections such as Hepatitis B and C, malaria, and syphilis are not routinely screened [30313233]. As a result, some of the blood being transfused is likely to contain unscreened pathogens.

Although the prevalence of HBsAg among the blood donors in sub-Saharan Africa considered as high, the possibility of underestimation of the prevalence may not be ruled out completely. The diagnostic techniques often used identify HBV infected donors through the detection of HBsAg are known to be reasonably reliable. However, several circumstances which can lead to HBV infectious donations entering the blood supply have been identified [34], these include; (i) collection of donations during the infectious 'window period' following infection when tests in use are unable to detect the infection; (ii) donations testing falsely negative due to test sensitivities less than 100%; (iii) donations falsely issued as negative due to an error in sampling, testing, recording of test results, or removal of positive donations; (iv) donations collected from individuals with fluctuating or waning levels of hepatitis B surface antigen (HBsAg) during later stages of HBV carriage. Furthermore it has been demonstrated that transmission by blood components negative for HBsAg can still occur during chronic stages of infection (i.e. "occult" HBV infection, OHB). OHB is defined as the presence of HBV DNA in blood or liver tissues in patients negative for HBsAg, with or without any HBV antibodies [35]. Because of limitations in current blood screening practices in sub-Saharan Africa, OHB is an overlooked source of HBV transmission. This problem is compounded by the fact that in most developing countries particularly in Africa, screening of HBV in blood donors is limited to HBsAg testing.

Furthermore, blood donors infected with HBsAg mutants and those circulating low level of viral protein may escape detection by screening assay and therefore, may affect the safety of blood supply [36]. Another explanation is that virus variants yield sequences that are not recognized by the antibodies employed in the assays [37]. There are variants in other parts of the genome that down regulate the production of HBsAg [38]. Occasionally, a superinfection with hepatitis C virus (HCV) may induce clearance of hepatitis B. This could be due to the dominant role of HCV in eliciting an immune response [39]. Antibodies to hepatitis B core (HBc) antigen are marker of acute, chronic, or resolved HBV infection and remain detectable for life. These can be present in the absence of both HBsAg and anti-HBs antibodies, during the convalescent period following acute hepatitis B before the appearance of anti-HBs antibodies, or in patients who resolved infection but lost detectable anti-HBs antibodies. Anti-HBc is therefore detected in anyone who has been infected with HBV [40]. It has been demonstrated that some HBsAg negative individuals and those positives for anti-HBc continue to replicate HBV [4142]. These findings suggest that recovery from acute hepatitis B virus infection may not result in complete virus elimination, but rather the immune system keeps the virus at a very low level. A positive correlation has been shown between anti-HBc titre and detection of HBV-DNA in serum samples of HBsAg negative individual [43]. Hence many of the cases of HBV infection in sub-Saharan Africa in individuals with blood transfusion history may have resulted from post-transfusion hepatitis B virus infection [44].

PUBLIC HEALTH CONSIDERATIONS

Since blood transfusion is an important part of modern medicine, the safety of blood and blood products remains a global issue. Although many countries screen all blood donations for a number of infectious agents, a significant proportion of the world's blood supply particularly in the developing countries is either unscreened or poorly screened, with the resultant risk to recipients of transfusion transmitted HBV infection. The substantial risk of transfusion transmitted HBV infection in many developing countries is a consequence of poorly developed healthcare systems and limited resources. In these countries, the safety of the blood supply is compromised frequently, either because of lack of resources with which to purchase screening assays, or because of acute blood shortages and insufficient time to screen blood prior to transfusion [45]. As part of public health interventional measures, the transmission of HBV can be minimized by the screening of donors prior to donation, exclusion of high-risk donors, followed by the in-vitro screening of donations for HBsAg (+anti-HBc in some countries) prior to transfusion. Infection control measures in health-care settings including safe injection practices and proper sterilization techniques of medical instruments and education of barbers about the significance of sterilization of

their instruments may reduce the burden of HBV infection particularly in low income settings with high HBV endemicity [46]. There is also an urgent need of developing locally relevant guidelines for counseling and management of HBsAg positive blood donors. It is important to encourage and actively support the introduction of appropriate screening programmes which can be based upon simple assay formats, such as agglutination, rather than the favoured but more complex enzyme immunoassays which are more expensive, require specific equipment and support, and take longer to perform [45]. Such approaches will help reduce greatly the transfusion transmission of HBV. However, since the residual risk of posttransfusion infection resides essentially in chronic infections with low viral load and HBsAg level, to ensure blood safety, HBsAg testing will require highly sensitive assays which would enable the identification of donors carrying low viral and antigen loads. Current enzyme immmunoassays (EIAs), but not rapid tests, appear adequately sensitive [23]. Policy for checking the collected blood unit by 3 tests for anti-HBc, anti-HBsAg and HBsAg should be reconsidered in favor of HBV-DNA testing by polymerase chain reaction, to possibly achieve the zero risk goal of transfusion transmitted HBV infection in settings that can afford this [47]. Accurate assessment of transfusion-transmitted HBV infection which necessitates knowledge about donation histories and person-years at risk is very essential in order to establish comprehensive frameworks for monitoring blood donations and infectious disease markers which remains a key to monitoring blood safety.

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