Hepatitis B Virus Genetic Diversity

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Abstract

Hepatitis B Virus (HBV) infection is a major health problem and may lead to chronic hepatitis, cirrhosis and Hepatocellular Carcinoma (HCC). Detecting hepatitis B virus variants and antigenic variation of the HBsAg in relation to different geographic areas and process of treatment is fundamental for laboratory assay design, vaccine formulation, and prediction of progression of disease to chronic hepatitis and HCC. Hepatitis B viral mutants may emerge as a result of immune response or treatment options. In this manuscript some aspects of hepatitis B virus genetic diversity would be reviewed.

Keywords: Hepatitis B Virus; Genotype; Mutation; HBV Variability

Introduction

Hepatitis B Virus (HBV) is a human DNA virus, which replicates through an RNA intermediate because of the Reverse-Transcriptase (RT) activity of its DNA polymerase. As a result, the mutation rate for HBV is higher than the rate observed for most DNA viruses. HBVs are classified into genotypes based on genomic sequencing, and antigenic subtypes based on the antigenic properties of its major surface glycoprotein, the HBV Surface Antigen (HBsAg). Subgenotypes have been identified within most of the HBV genotypes. The HBV groups defined by the different genotype-HBsAg subtype associations found over the world display characteristic geographical distributions, reflecting the movements of human populations and other epidemiologically significant events. Such HBV groups constitute genetically stable viral populations sharing a common evolutionary history, but additional stable changes, originating from mutation and mutant selection, are observed within all of them. These viral sub-populations are known as the HBV variants, and some of which have medical and public health relevance. Pre-core (pre-C) defective variants have been shown to make HBV infection much less susceptible to interferon treatment, and treatment failures with other antiviral drugs have been associated with selection of resistant variants that display specific mutations in the genome region encoding the viral RT activity. Since the RT region of the genome overlaps the sequence encoding the HBsAg molecule, selection of drug resistant variants involves, in some cases, the indirect selection of HBsAg variants. Viral variants displaying changes in HBsAg seem to be very common among chronic HBV carriers; and some of these variants may emerge under the pressure of the neutralizing antibody response, leading to vaccine resistance and resistance to immunotherapy. In addition, some of these HBsAg variants have been associated with lack of detection by HBsAg tests used for the diagnosis of HBV infection, for the identification of chronic carriers, for screening of blood donations for transfusion, and in the manufacture of therapeutic blood products [1]. The eight HBV genotypes identified display distinct geographical and ethnic distributions. For example, genotypes B and C are prevalent in Asia, while genotypes A and D are prevalent in Europe, United States and Central Africa. HBV genotypes and mutations represent candidate biomarkers for predicting risk of progressive disease and disease severity [2]. Iran is a low to medium endemic country for Hepatitis B Virus (HBV), depending on the region, where genotype D is dominant [3]. In a study, the 70 HBsAg test kits from around the world were evaluated comparatively for their clinical sensitivity, analytical sensitivity, sensitivity to HBV genotypes and HBsAg subtypes, and specificity using 394 (146 clinical, 48 analytical and 200 negative) International Consortium for Blood Safety (ICBS) Master Panel members of diverse geographical origin comprising the major HBV genotypes A-F and the HBsAg subtypes adw 2,4, adr and ayw1-4. Reduced sensitivity for HBsAg with genetic diversity of HBV occurred with genotypes/ subtypes D/ayw3, E/ayw4, F/adw4 and by 8 gene mutants. Specificity of the HBsAg assays was >or=99.5% in 57 test kits and 96.4-99.0% in the remaining test kits. Diagnostic efficacy of the evaluated HBsAg test kits differed substantially. Laboratories should therefore be aware of the analytical sensitivity for HBsAg and check for the relevant HBV variants circulating in the relevant population [4].

Carriers of hepatitis B virus genetic diversity

Understanding the prevalence of potential antigenic variation of the HBsAg is fundamental for assay design and to future changes in vaccine formulation. In a study, the nature and frequency of HBsAg polymorphisms occurring in France in chronic carriers and in newly diagnosed patients were determined. With focused on variations in the Major Hydrophilic Region (MHR), the central core of HBsAg known to be exposed on the surface and involved in antibody binding.

The global frequency of MHR variants was 27.8%. In multivariate analysis, the independent variables associated with MHR variants were advancing age and the presence of genotypic resistance to nucleoside or nucleotide analogues. Variation of the MHR may serve to restore virus replication of resistant strains. Combined envelope and polymerase variants could impair diagnostic assays and limit treatment alternatives [5]. Occult hepatitis B is defined by the presence of Hepatitis B Virus (HBV) DNA in the serum in absence of Hepatitis B Surface Antigen (HBsAg). Studies were conducted to screen for occult HBV infection among family members of HBV carriers, incidentally detected positive for HBV infection with a view to assess the pattern of virus transmission among them.

Although majority of the occult infection was associated with low
viral load, 3/15 (20%) cases were with higher viral load and potential infectivity. These cases are especially notable in diagnostic, blood banking, and transplantation services [6].

Chronic carriers of Hepatitis B Virus (HBV) usually show Hepatitis B Surface Antigen (HBsAg) in their sera, which is considered the best marker for acute and chronic HBV infection. In some individuals, however, this antigen cannot be detected by routine serological assays despite the presence of virus in liver and peripheral blood. One reason for this lack of HBsAg might be mutations in the part of the molecule recognized by specific antibodies. To test this hypothesis, the HBV S gene sequences were determined of isolates from 33 virus carriers who were negative for HBsAg but showed antibodies against the virus core (anti-Hbc) as the only serological marker of hepatitis B. Isolates from 36 HBsAg-positive patients served as controls. In both groups, a considerable number of novel mutations were found. These findings suggest that at least some of the chronic low-level carriers of HBV, where surface antigen is not detected, could be infected by diagnostic escape mutants and/or by variants with impaired replication [7].

The hepatitis B virus replicates via an error prone viral reverse transcriptase resulting in a large pool of quasispecies with mutations spread throughout the genome. During antiviral drug selection pressure (e.g., lamivudine, adefovir, or entecavir) HBV mutants are selected from the pre-existing pool of quasispecies and over time become the dominant species. Not all mutations result in replication competent virus as HBV has the added complexity of overlapping reading frames. The HBV polymerase (Pol) gene overlaps the hepatitis B surface antigen (HBsAg) in a frame-shifted manner with the result that drug-resistant mutations in the HBV Pol can directly impact on the nature of HBsAg and its function. HBV genomic databases have been established to monitor antiviral selected mutations and are useful in determining conserved residues, genotypic differences, polymorphisms, and the mutation profiles selected under different antiviral selection pressures. These HBV databases may aid in the development of new diagnostic reagents as well as the monitoring of polymerase and envelope mutations selected under different antiviral pressures. Antiviral drug resistant mutants emerge as a function of at least six factors: the viral mutation frequency, the intrinsic mutability of the antiviral target site, the selective pressure exerted by the drug, the magnitude and rate of virus replication, the overall replication fitness of the mutant, and the availability of replication space. Clearly, improved treatment strategies are required urgently to prevent the continued selection of HBV drug-resistant mutants [8]. In a survey of five provinces in China, the overall HBV infection rate in the general population was found to be 42.6%, with 10.3% testing positive for Hepatitis B Surface Antigen (HBsAg). The pattern of age distribution suggests that horizontal transmission is an important route of HBV infection during early childhood, and the proportion of chronic HBsAg carriage attributable to perinatal transmission has been estimated at only 13-20%. Contact with infected family members probably accounts for much of the horizontal transmission in children [9].

Hepatitis B virus genetic diversity and vaccine formulation

In a study a compartment model expressed by a set of partial differential equations based on the characteristics of HBV infection is described. According to that model, if all newborns are vaccinated according to schedule, the rate of HBV carriage will decline sharply over time to 0.2% in 70 years. Thus, the key to controlling and eliminating HBV transmission in China is to find ways to immunize all infants throughout the country, especially in poor, rural areas [10].

A model was developed to calculate the age-specific risk of acquiring HBV infection, acute hepatitis B (illness and death), and progression to chronic HBV infection. In the surviving birth cohort for the year 2000, the model estimated that without vaccination, 64.8 million would become HBV-infected and 1.4 million would die from HBV-related disease. Routine infant hepatitis B vaccination, with 90% coverage and the first dose administered at birth would prevent 84% of global HBV-related deaths. Globally, most HBV-related deaths result from the chronic sequel of infection acquired in the perinatal and early childhood periods. Inclusion of hepatitis B vaccine into national infant immunization programs could prevent >80% of HBV-related deaths [11]. In a study, the estimated annual incidence of HBV infection in England and Wales was 7.4 per 100,000. Injecting drug use was the most frequently reported route of transmission. The UK prevalence of HBV infection is dependant on global rather than national immunization policy. Endemic transmission may be reduced by improving immunization coverage among injecting drug users, which is expected to also reduce the number of cases without a risk factor reported. In addition, immunization options that better suit the needs of ethnic minorities need to be explored [12]. Studying the nucleotide sequence of the S-gene of HBV from 63 Dutch blood donors, considerable variation was found. The majority of the donor strains (83%) appear closely related to local HBV isolates as present in intravenous drug users, immigrants, and homosexual men. The remaining 11 (17%) HBV strains belong to various non-Western genotypes. This supports the policy in low endemic countries to limit vaccination to at-risk groups. On the other hand, it must be realized that, after 20 years of vaccination of at-risk groups, HBV still circulates in the at-risk groups and Dutch blood donors acquire the HBV strains involved [13].

The Solomon Islands is a multi-ethnic nation with a high rate of Hepatitis B Virus (HBV) infection. Asymptomatic populations from the Western Province were enrolled. The positive rate for HbsAg was 21.5%. The major Melanesian genotype was C (HBV/C), whereas the major Micronesian genotype was D (HBV/D). The prevalence of Hepatitis B e antigen (HBeAg) in serum was lower in carriers of HBV/D than of HBV/C. While the prevalence of the BCP mutation (T(1762)A(1764)) tended to be higher in HBV/C, that of the Pre-C mutation (T(1846)) was significantly higher in HBV/D (P < 0.0001). HBV infection in the Solomon Islands is hyperendemic, and the genotype is ethnicity-specific. HBeAg appears to clear from the serum in young adulthood in HBV/D infection, which may be influenced by genotype-dependent features in relation to viral mutations [14].

In an attempt to evaluate the long-term immunogenicity and efficacy of plasma-derived hepatitis B vaccine in preventing hepatitis B virus infection, 199 infants born to hepatitis B e antigen-positive hepatitis B surface antigen–carrier mothers were found to be antibody to HBsAg-positive (greater than or equal to 10 mIU per ml) 2 months after the first booster of hepatitis B vaccination at age 1, and their serum HBsAg and anti-HBs were checked annually to ages 3 to 5. Of the nine infants whose initial anti-HBs were low (10 to 100 mIU per ml) in concentration, four (44%) were found to be anti-HBs seronegative at age 3, while none of the 127 vaccine responders with high anti-HBs levels (greater than 1,000 mIU per ml) lost their anti-HBs during the 4-year follow-up period. Whether the vaccine responders lost their anti-HBs or not, no hepatitis B virus infection occurred in these vaccinees during the follow-up period. Thus, in the first 5 years of life, the protective efficacy in the high-risk infants who responded to plasma-derived hepatitis B vaccine was 100% [15]. The cases of early Hepatitis B vaccine adoption in Taiwan and Thailand are used to explore the
relevance of explanatory factors identified in the literature as well as the need to go beyond a variable-centric focus by highlighting the role of policy context and process in determining the pace and extent of adoption. The cases suggest the feasibility and importance of modeling 'causal diversity' - the complex set of necessary and sufficient conditions leading to particular decisional outcomes in a broad range of country contexts [16].

Serologic testing for hepatitis B virus (HBV) surface antigen (HBsAg) and antibody to HBV core antigen (anti-HBc) has historically been the foundation of blood screening, while HBV Nucleic Acid Testing (NAT) was recently developed to detect HBsAg-negative, anti-HBc-negative blood units donated during early acute infection. In countries that do not screen for anti-HBc, HBsAg testing would be the only means of detecting donations from chronically infected individuals with low/intermittently detectable DNA, since even single-donor NAT would not identify these potentially infectious blood units. In the future, the current fully automated HBsAg assays may incorporate significant sensitivity improvements, and automated single-sample HBV NAT may become a reality. Each country will need to develop its blood screening strategy based on HBV endemicity, yields of infectious units detected by different serologic/NAT screening methods, and cost effectiveness of test methods in ensuring blood safety [17].

Over the last 20 years, HBsAg variants have been involved in important medical and public health issues, such as vaccine escape, failure of hepatitis B immune globulin to protect liver transplant patients and babies born to carrier mothers, and failures in detection of HBV carriers. Mutants involved in vaccine escape and in immune therapy failure are selected under the pressure of specific antibody and may be naturally transmitted to susceptible individuals, and thus may spread among the population. Recent data suggest that the prevalence of such HBsAg variants among random chronic carriers could be as high as 6–12% for publication, and that prevalence increases with time of such HBsAg variants among random chronic carriers could be as high as 6–12% for publication, and that prevalence increases with time.

Conclusion

Detecting hepatitis B virus variants and antigenic variation of the HBsAg is fundamental for assay design, vaccine formulation, and progress to chronic hepatitis and Hepatocellular Carcinoma (HCC).

References