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THE EPIDEMIOLOGY, CLINICAL OUTCOME AND RESPONSE TO ANTIVIRAL THERAPY FOR DIFFERENT HEPATITIS B VIRUS GENOTYPES

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Abstract:

Hepatitis B virus is a crucial public health problem in Pakistan. It has been classified into eight genotypes (A-H) based on genome sequence divergence. Hepatitis B virus genotypes have distinct geographical distributions. Recently genotypes of hepatitis B have received a lot of attention due to its clinical as well as therapeutic importance. In this review, we will discuss the epidemiology, clinical outcome and response to antiviral therapy for different hepatitis B virus genotypes.

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INTRODUCTION:

Hepatitis B virus infection is a global health problem with its continuously increasing morbidity and mortality in the developing countries like Pakistan. Despite the presence of hepatitis B vaccine, new Hepatitis B virus infection remains common. Worldwide, 350 - 400 million people are estimated to be persistently infected with hepatitis B virus and three-quarters of these people reside in Asia. According to WHO (World Health Organization), Pakistan falls under the endemic region with 3% HBV (hepatitis B virus) infected country population [1-3].

Long-term infection increases the risk of developing cirrhosis and hepatocellular carcinoma with approximately 1 million Hepatitis B virus-associated deaths from hepatocellular carcinoma every year [1]. Most acute infections with hepatitis B virus are self-limited with clearance of virus and development of immunity. However, an estimated 5% to 10% of adults and 85% to 95% of children develop chronic Hepatitis B virus infection [2]. Studies indicated that the hepatitis B is a crucial public health problem in Pakistan with increased morbidity and mortality. Exposure rate of Hepatitis B virus in Pakistan is not known clearly but limited data shows 35-38% prevalence with 4% being carriers and 32% having anti-Hepatitis B virus surface antibodies through natural conversion [3].

Currently hepatitis genotyping is emerging as a useful additional test that may add additional information and understanding of the natural history of hepatitis B virus. Recently several different Hepatitis B virus genotypes have been discovered and received a lot of attention regarding their epidemiology, clinical implications and response to antiviral therapy. A problem in introduction of genotyping to clinical practice in the developing world is the lack of a simple, rapid and accurate test. Hence, despite the much progress in understanding the natural history of hepatitis B virus infection, we still have a long way to go before we can conquer hepatitis B virus infection.

Molecular Epidemiology of HBV Genotypes and its Geographic Distribution

Hepatitis B virus is the smallest known DNA virus, and its partially double stranded circular genome consists of four overlapping genes encoding the viral envelop (pre-S and S), nucleocapsid (precore mutations and core promoter mutations), polymerase with an error- prone reverse transcriptase activity, and X protein. Due to differences in the nucleotide homology of the surface gene there are different Hepatitis B surface antigen serotypes [4].

Several methods have been developed and used to analyze hepatitis B virus genotyping which include, direct sequencing, PCR (Polymerase Chain Reaction) based restriction fragment length polymorphism (RFLP), line probe assay and enzyme-linked immunoassay. Recently a new genotyping method, based on PCR amplification assay using type-specific primers has been developed. Although the most common method for HBV genotyping is by PCR-RFLP technique, but it is reported that HBV genotyping by multiplex PCR is more sensitive than genotyping system using RFLP analysis.

Leblebicioglu reported that nested PCR methodology for HBV genotyping is 1000-fold more sensitive than PCR-RFLP [5-9]. At present, hepatitis B virus has been classified into 8 genotypes (A-H) based on intergroup divergence of 8% or more in the complete nucleotide sequence [10,11].

There is some evidence that the long-term prognosis, the initial clinical picture, and the response to treatment may differ depending on which genotype has infected the patient. Genotypes and sub-genotypes of Hepatitis B virus have different geographic distribution in the world (Table 1 and 2) [10,11].

Table No 01: Genotypes of Hepatitis B virus and Geographic Distribution

GENOTYPE	GEOGRAPHIC DISTRIBUTION
A	Africa, India, Northern Europe, United States
B	Asia, United States
C	Asia, United States
D	India, Middle East, Southern Europe, United States
E	West and South Africa
F	Central and South America
G	Europe, United States
H	Central and South America, California in United States

Table No 02: Sub genotypes of HBV and Geographic Distribution

Genotype	Geographic Distribution
A1 (Aa)	Asia & Africa: India, Nepal, Philippines, Japan, South Africa
A2 (ae)	Europe & North America: UK, Germany, France, USA, Poland
B1 (Bj)	Japan
B2 (Ba)	Asia: Taiwan, China, Vietnam
B3	Indonesia
B4	Vietnam
C1 (Cs)	East Asia: Taiwan, Japan, Korea, China
C2 (Ce)	South East Asia: China, Hong Kong, Malaysia, Bangladesh, Thailand, Vietnam
C3	Polynesia
C4	North East Australia

Prevalence of HBV Genotypes in Pakistan

Baig S, reported Genotype D as a dominant genotype followed by A and mixed A and D in Pakistan [12]. In Karachi 180 chronic Hepatitis B surface antigen positive young females were tested for genotypes by Hakim ST et al [3] revealed genotype D in 151 (84%) and mixed infection with B and D in 28 (16%). In a similar type of another study conducted by Masroor Alam et al, who tested 110 individuals positive for Hepatitis B virus infections indicated the highest prevalence of genotype D (65%), followed by genotype B (27%), A (5%) and co infection with multiple genotypes (3%) [13].

Another study was done in Pakistan to determine the prevalence of hepatitis B virus genotypes in patients with chronic hepatitis B infection. That study reported genotype C as the most dominant genotype in all their cases, appearing in 41% patients. Further provincial breakup of the same study reported predominant prevalence of Genotype A (68%) in Sindh; genotype C (69%) in North West Frontier Province, whereas genotypes C and B were dominant in Punjab (40% and 26% respectively) [14].

Influence of HBV risk factors on HBV Genotypes

A study conducted among injecting drug users in Pakistan showed presence of genotype D in 62%, genotype A in 9% while 29% individuals were found to be infected with a mixture of genotype A and D [15]. Genotypes A and D were most prevalent in HIV-HBV co-infected patients in Madrid, Spain. HBV subtype A was present among three-fourth of patients infected through sexual contact (homosexual), whereas the same percentage of subtype D was isolated among injection drug users ($P < 0.001$) [16].

Influence of HBV Genotypes on Clinical Manifestation

Genotype A was found to be more strongly associated with severe liver disease in Pakistan [12]. Kumar et al [17] reported that genotype A is more often associated with alanine aminotransferase (ALT) elevation, core antigen positivity, absence of anti-Hepatitis Be in patients aged 25 years and above, and genotype A was more frequently associated with cirrhosis of liver as compared to genotype D.

Many prospective, case-controlled and cross-sectional studies conducted among the patients with hepatitis B virus infection predominantly, but not entirely, indicate that, genotype B is associated with spontaneous Hepatitis Be antigen seroconversion at a younger age, less active liver disease, and a slower progression to cirrhosis and hepatocellular carcinoma as compared to genotype C. Further, the patients were less likely to have hepatitis flares and more likely to remain in remission after Hepatitis Be antigen seroconversion [18-21].

In a cross-sectional study of 694 patients with hepatitis B virus infection in United States of America revealed that the genotypes B and D are associated with lower prevalence of hepatitis Be antigen than genotype A; while genotype B was associated with lower rate of hepatic decompensation as compared to genotypes A, C and D [22]. In Thailand, alanine aminotransferase (ALT), HBV- DNA and Hepatitis Be Antigen positivity were significantly higher in carriers infected with genotype C than in those infected with B [23]. It

is interesting to know that hepatocellular carcinoma in Japan occurs less frequently with genotype B and occurs at an older age. It is believed that shorter duration of high level of Hepatitis B virus replication and less active necro-inflammation may contribute to a more favorable outcome among patients with genotype B. There is only one study from Taiwan that contradicts this belief; in this study, genotype B was more frequently encountered in patients with hepatocellular carcinoma aged less than 50 years (90% in those aged less or equal to 35 years) [24].

Pathologically, genotype B patients had a higher rate of solitary tumors (94% vs. 86%; P = 0.048) and more satellite nodules (22% Vs 12%; P = 0.05) compared with genotype C patients [6]. In another study, HBV - DNA levels in cell lysates were highest for type C, followed by Bj/Ba and D/Ae (P < 0.01). HBV - DNA levels were lowest for type Aa (P < 0.01) [7]. These findings were consistent with early and severe complications with genotype C. Among male Taiwanese, genotype C was associated with a five-fold increased risk of hepatocellular carcinoma compared with all other genotypes. Effects of genotype C and increased viral load were additive in the same study; men carrying genotype C who had a high viral load had nearly 26.5 times the risk of developing Hepatocellular carcinoma [8]. Genotype C was also more prevalent in patients with cirrhosis [24]. Genotype F was found in 68% of patients with HCC, compared to 18% of individuals without hepatocellular carcinoma (P < 0.001) in Alaskan Native People with chronic HBV [25].

Influence of HBV Genotypes on Antiviral Therapy

The response to antiviral therapy in hepatitis B virus infection is influenced by many host and viral factors. Recently, hepatitis B virus genotypes have attracted increasing attention since they influence the activity and outcome of Hepatitis B virus - associated chronic liver disease, as well as the response to antiviral therapies.

Lamivudine

Since its approval in 1998, Lamivudine has gained wide popularity for the treatment of chronic hepatitis B due to high efficacy with minimal untoward effects. Kao et al [26] reported good response to Lamivudine in patients treated for 6-30 months infected with genotype B compared with C. Chien et al, [27] reported much higher sustained response to Lamivudine in patients infected with genotype B as compared with genotype C. Other studies indicated that genotype D is more likely to have significantly higher sustained viral response (SVR) after Lamivudine therapy as compared to genotype A [28]. Another study based on 78 German patients reported that Lamivudine- resistant mutants emerged more rapidly with genotype A as compared to genotype D [29].

INTERFERON

Hepatitis B virus genotypes have been reported to correlate with response to interferon. Studies suggested that genotype B and A had a higher rate of Hepatitis Be antigen seroconversion compared to genotype C, D or E [30-31]. Peg-interferon α-2b is the best therapy to achieve Hepatitis B surface antigen clearance in patients with genotype A [32]. Recent studies with pegylated interferon (IFN) confirmed that hepatitis Be antigen seroconversion occurred more often with genotypes A (47%) and B (44%) as compared to genotypes C (28%) and D (25 %) [33].

Erhardt et al reported higher sustained response (six months after treatment) to standard interferon alfa (IFN) therapy in hepatitis B virus genotype A compared with hepatitis B virus genotype D infected patients (49% Vs 26%) p < 0.005. He further concluded that the sustained response to IFN for HBV genotype A compared with HBV genotype D was 46% Vs 24% (p < 0.03) in Hepatitis Be antigen positive (n=99) and 59% Vs 29% (p <0.05) in Hepatitis Be antigen negative (n=45) patients [34].

THYMOSIN ALPHA-1 THERAPY

Genotype, presence of precore mutation and thymosin alpha-1 therapy were independently predictors to complete response. Genotype B compared to genotype C, is associated with a higher response rate to thymosine alpha-1 therapy [35].

CONCLUSION:

Hepatitis B virus genotypes influence the severity of liver disease and response to interferon and lamivudine therapies. Severity and outcome of chronic hepatitis B are more serious in patients infected with genotype C and A as compared with genotype B. Evidence indicates a better response to interferon in patients infected with genotype A and B as compared with genotype C or D; whereas, the response to Lamivudin was better in patients infected with genotype B and D rather than genotype A or C. Patients with Hepatitis B virus genotype A tended to be more likely to have lamivudine resistance mutations and to develop resistance earlier.

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