

Genetic Diversity of HBV Genotypes/ Subgenotypes and Their Correlation with Disease Progression

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ABSTRACT

Hepatitis B virus (HBV) infection remains a global health problem and a public health threat in the present era. It is estimated that 2 billion people are infected with HBV and 350 million people suffer from chronic HBV infection in the world. India is a prosperous country in Asia and has peculiar geographical presence which is responsible for evasion of this land by traders and invaders in past and resulted in gene influx due to invasion and/or anthropological migrations in the past. Moreover, recent increase in trade, trafficking and use of illicit drugs has also considerably influenced the epidemiology of HBV in different parts of India. However, data on the genotypes/subgenotypes diversity of HBV in India is scanty. In this manuscript, the information available on the genetic diversity of HBV genotypes and subgenotypes in India and in world and their relationship with the disease progression has been reviewed.

Abbreviations: HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; LC: Liver cirrhosis; RFLP: Restriction fragment length polymorphism; ORF: Open reading frame; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; PCR: Polymerase chain reaction, ELISA: Enzyme-linked immunosorbent assay; ALT: Alanine aminotransferase; IFN: Interferon; PEG-IFN: Pegylated IFN.

Keywords: Hepatitis B virus, Genotype, Subgenotype, Serotype, Interferon- α , Lamivudine, Adefovir dipivoxil.

INTRODUCTION

Hepatitis B virus (HBV) is one of the major global public health problems leading to significant morbidity and mortality worldwide. HBV infection is the 10th leading cause of death worldwide and HBV-related hepatocellular carcinoma (HCC) is the 5th most frequent cancer worldwide.⁵⁷ HBV infection is associated with a diverse clinical spectrum of liver damage ranging from asymptomatic carriers, chronic hepatitis, liver cirrhosis and HCC.⁷² Hepatitis B is caused by HBV. An estimated 350 millions are chronically infected with HBV and approximately 1 million persons die annually from HBV-related chronic liver diseases, including severe complications, such as liver cirrhosis (LC) and HCC.²¹¹

The world can be divided into three areas where the prevalence of chronic HBV infection is high (> 8%), intermediate (2-8%) and low (2%).¹²⁶ High endemic areas include Africa, Southeast Asia, the Middle East (except Israel), Southern and Western Pacific islands, the interior Amazon river basin and certain parts of the Caribbean (Haiti and the Dominican Republic). The prevalence of chronic HBV infection is intermediate (2-7%) in South Central and Southwest Asia, Israel, Japan, Eastern and Southern Europe, Russia, most areas surrounding the Amazon river basin,

Honduras and Guatemala. The prevalence of chronic HBV infection is low (< 2%) in the general population in Northern and Western Europe, North America, Australia, New Zealand, Mexico and Southern South America.³⁵

HBV GENOME

HBV is a member of *hepadnaviridae* family;¹⁸⁷ a family of enveloped DNA virus with partially double-stranded DNA genome of approximately 3.2 kb length, circular genomes that replicates by reverse transcription.⁷⁹ The HBV genome encodes four partially overlapped open reading frames (ORF): The surface (preS1, preS2, S), core (precore, core), polymerase and the 'X' gene, respectively.^{71,173}

HBV GENOTYPE

A genotype is generally defined as the genetic constitution of an organism. In case of HBV, genotypes are defined by an intergroup divergence in the complete HBV genome sequence of more than 8%^{150,156} and 4% at the level of the S gene.¹⁵¹ There are eight genotypes of HBV: A, B, C, D, E, F, G and H.

Early studies enabled the identification of four genotypes A to D¹⁵⁵ with the other genotypes E,¹⁵³ F,^{146,151,153} G,¹⁹³ and H¹⁴ being identified later. Recently, Arankalle et al¹¹

reported genotype I from the Idu Mishmi primitive tribe of Northeast India. A new genotype of which is divergent from known human and ape genotypes isolated from a Japanese patient was provisionally assigned to new genotype J.¹⁹⁵

HBV SUBGENOTYPE

Subgenotype be used to identify subgroups dividing the HBV genotypes and between 4 and 8% intergroup nucleotide difference across the complete genome. The term clade may be confined to identify division showing less than 4% nucleotide difference within subgenotypes. Moreover, because the geographical distribution of the various subgenotypes was not clearly demarcated, numbers 1, 2 were suggested instead of Roman numerals or letters representing areas of the world. For example, the unique segment of genotype A, previously called subgroup 'A' that was identified in South Africa²⁹ should be referred to as subgenotype A1 instead of Aa ('a' for Africa/Asia).¹⁸⁹ Similarly, subgroup Ae ('e' for Europe/elsewhere)¹⁹¹ should preferably be referred to as subgenotypes A2, B1 and B2, respectively. Moreover, the two clades 1 and 2, identified within genotype F, could be referred to as subgenotype F1 and F2, respectively.¹⁴⁹

Subgenotypes (subgroups) have been identified for certain HBV genotypes.^{38,83,103,143,152,167} HBV/C has been classified into five subgenotypes, HBV/C1 to HBV/C5,^{38,83,167,190} HBV/D into HBV/D1 to HBV/D5.^{21,31,152,172} Similarly, HBV/B was initially classified into two subgroups, Bj and Ba.¹⁹⁷ Subgroup Bj is found mostly in East Asia, including Japan, while subgroup Ba is found throughout Asia and has recombination with HBV/C in the C gene.¹⁹⁷ More recently, subgroup Ba has been further divided into four subgenotypes, HBV/B2 to HBV/B5, with subgroup Bj being renamed subgenotype HBV/B1.^{143,167,190}

HBV SUBTYPES OR SEROTYPES

Based on the antigenic heterogeneity of the HBsAg, four serological subtypes or serotypes are identified initially. These are adw, adr, ayw and ayr where 'a' is defined as the common determinant for all four serotypes. There are two alleles of the 'a' determinant, I and t, specified by Thr and Ile at position 126, respectively. These are separated from the two mutually exclusive subdeterminants d/y and w/r.^{18,107} Amino acids substitutions at positions 122 and 160 of the HBsAg are responsible for the expression of the d/y and w/r specificities, respectively.¹⁵⁵ With the description of additional subdeterminants of 'a', the number of serological subtypes increases to nine: ayw1, ayw2, ayw3, ayw4, ayr, adw2, adw4, adrq⁺ and adrq⁻.¹²⁵ An intermediate

between ayw3 and ayw4 has also been identified.¹⁰⁵ The q determinant is originally described to be present in all serological subtypes except adw4,¹²⁴ but is later found to be absent from adr strains in Pacific region, thus delineating adr into either q⁺ or q⁻.⁵⁰ Various amino acids differences in the HBsAg have been identified between the different serological subtypes.¹⁵⁰

A geographical pattern for the distribution of subtypes is confirmed. Their geographical distribution is found to be stable over two decades. The subtype ayw is described in the Mediterranean countries (ayw2, ayw3), in West and Central Africa (ayw4, ayw2) and in Vietnam (ayw1). The rare subtype ayr is found in Vietnam. The subtype adw is predominant in North-West Europe, in America, in East and South Africa, in India (adw2) and in South-East Asia (adw4). The subtype adr can be found in Polynesia (adrq⁻) and in South-East Asia (adrq⁺).⁵¹

DETERMINATION OF HBV GENOTYPE

There are several methods for HBV genotyping¹²⁷ which are described as follows:

1. *Direct sequencing*: PCR amplifications of pre-S or S region are done by using pre-S or S region primers. The amplified products are directly sequenced and then sequences are compared against published sequences to determine homology with known genotypes.
2. *Restriction fragment length polymorphism (RFLP)*: Samples are first amplified by using the S gene primers. The amplified PCR products containing genotype-specific regions are then digested by restriction enzymes. Finally, the HBV genotype is differentiated based upon differences in the sizes of the digested fragments.
3. *Line probe assay*: Amplicons of the S gene are hybridized to strips precoated with genotype-specific oligonucleotide probes. Determination of HBV genotypes is based on the pattern of reactive bands.
4. *Enzyme-linked immunosorbent assay (ELISA)*: Monoclonal antibodies to genotype-specific epitopes of the pre-S2 region are employed.

GEOGRAPHICAL DISTRIBUTION OF HBV GENOTYPES

HBV genotypes show varying geographic distribution worldwide. Genotype A is prevalent in Europe, Africa and India.¹¹⁷ HBV genotype B and genotype C are predominant in most part of Asia, including China, Japan and Indonesia.^{60,117,121,139,154,159,171} The HBV genotype D is common in the Mediterranean area, the Middle East and India. The genotype E of HBV is found in sub-Saharan Africa and India.^{57,68,103,117,159,182,220} The HBV/F and

HBV/H is only identified in Central and South America.^{14,68,117,144} The HBV/G has been found in France, Germany and United States.^{47,56,117,205} Recently, Arankalle et al¹¹ observe genotype I from the Idu Mishmi primitive tribe of Northeast India. A new genotype of which is divergent from known human and ape genotype isolated from a Japanese patient is provisionally assigned to new genotype J.¹⁹⁵

DISTRIBUTION OF HBV GENOTYPE AND SUBGENOTYPE WORLDWIDE

Genotypes C, D, E, G and C/G mixture were observed in Chinese Han patients with chronic hepatitis B.¹¹¹ Subgenotype Ba was a predominant subgenotype of HBV/B in patients with chronic HBV infection from Beijing, Shijiazhuang, Wenzhou and Shenzhen of China.²⁰⁸ Genotypes A, B, C and D were found in Yunnan province, China. Genotypes B and C predominated and C was the most prevalent genotype in Yunnan province, China.²¹⁷ HBV genotypes C and B were found in the Eastern China.¹⁹⁴ HBV subgenotypes Ba, C1 (Cs) and C2 (Ce) were the most prevalent subgenotypes in China.²¹⁰ Genotypes D, B, C and coinfection of genotypes B/D, C/D, B/C/D were detected and genotype D predominated in Uighur patients with chronic hepatitis B in Xinjiang province of China.¹²⁰ The HBV/C1 was only found in the patients originating from Southern China.²¹⁸ Genotypes C and B were predominant genotype followed by genotype B/C and D in China.⁶⁰ HBV genotype B was identified in all patients with CHB from different nationalities in ethnic minority areas in Yunnan province, China.²⁵ Genotype C was the major genotype followed by genotypes B, D and A in Changchun, China.⁸¹ In Bangladesh, the predominant genotypes were D and C. Overall, genotypes D, C, mixed C + D, A and B were found.¹²⁸ HBV genotype popularity in Shenzhen area was genotype B first and genotype C as the second.²¹⁹ The prevalence of genotypes B and C was found in China. Among HBV/C, subgenotypes Cs/C1 and Ce/C2 were found. Genotype C was prevalent genotype followed by genotype B and genotype B/C coinfection in Northern and Southern China.¹⁸⁵ HBV carriers in and around Hangzhou city, Zhejiang province, China showed the existence of genotypes A, B, C, D, mixed B and C and an absence of E and F genotypes.²²⁷ Genotype C was prevalent genotype followed by B and B/C. In genotype C, subgenotype C1 and subgenotype C2 were found. In genotype B, subgenotype Ba and subgenotype Bj were found from HBV-infected patients from Beijing, Changchun, Hanchuan Shenzhen, Qingyuan and Nanjing (China).¹¹⁰ HBV genotype C (subgenotype Ce and subgenotype Cs) was the

prevalent genotype followed by genotype B in Hong Kong.³⁹ Genotypes B, C and BC combination existed in Hubei province and genotype B was the major genotype in this area, especially in FHF and HCC patients.¹⁰⁹ Genotype C was predominant genotype followed by genotypes B and D in Lanzhou, China.¹⁸⁰ HBV genotypes B and C were the major genotype followed by genotype D in Guangdong province of China.⁶⁷ Genotypes B and C were found in Guizhou, China with genotype B as the major genotype. Genotype C was found more frequently in Han than in Dong and Miao minority in China.⁵⁷ Genotypes B and C were the predominant genotypes followed by genotype D in the Foshan area, China.²¹⁴ Genotypes B and C were found in Guizhou area of China.¹⁶⁴ Genotype B was predominant genotype followed by genotypes C, D, F and A in HBV DNA positive patients in Shenzhen, China.⁵² HBV genotypes B, C, D were observed in Guangzhou, China.²²³ Genotypes B and C were found in Changzhou area, China.²⁰⁹ Genotypes C, B and D were found in intrauterine transmission of HBV in Guangzhou, China.⁷⁵ Genotypes B and C were found among chronic HBV-infected patients in Hong Kong.³⁶ Genotype B was predominant genotype followed by genotypes C and D among the HBV carriers in Guangzhou province of China.²¹⁵

Genotypes D, C and A were found in the two largest provinces of Pakistan: Punjab and Sind. The D1 subgenotype was prevalent followed by D2, C2 subgenotypes.⁵ Genotype D (subgenotypes D1 and D3) was the most prevalent genotype followed by genotypes A and a mixture of A and D (AD) in Pakistani HBV strains.¹⁶ Genotype D appeared to be the dominant genotype among females in Karachi, Pakistan.¹⁴⁸ Genotype D was the most prevalent genotype followed by genotype A and mixed genotype (A/D) in Pakistan.¹⁷ Genotypes A, B, C and D were found from Pakistan and genotype C was the predominant. Genotypes B and C were predominant in Punjab and NWFP (North West Frontier Province), whereas genotype A was predominant in Sindh of Pakistan.⁸⁴

Genotype C (subgenotype C1) was the predominant strain followed by genotype B (subgenotypes B2, B3 and B4) among migrant workers from Cambodia, Laos and Myanmar in Thailand.¹⁷⁰ HBV genotype C was highly predominant followed by genotype B, mixed infection of genotypes B and C and genotype A in Northern Thailand.⁸⁷

The HBV genotypes B and C were found in Taiwanese HBV carriers.¹¹⁵ Genotypes A, B, C, mixed genotypes A and B, genotypes B and C, genotypes B and D, genotypes A and C and mixed infections of genotypes A, B and C were found in HBV-infected intravenous drug users (IVDU) in Taiwan.⁴⁴ HBV genotype B was main genotype followed

by genotype C in children with chronic HBV infection and HCC in Taiwan.¹⁴⁷ The prevalent genotype of HBV was genotype B in Taiwan.¹¹⁹ Genotypes A, B, C and D of HBV were found in Southern Taiwan.¹⁰⁸ In Taiwan, all adr HBVs were genotype C. Of the adw HBVs, genotypes B, C, F and A were observed.¹¹⁴

Genotypes A, D and F as well as the subtypes adw, ayw and adw4 were found in a cohort of patients in a hospital in Porto Alegre, South of Brazil.²³ HBV genotypes A, F and D were observed and genotype A was the most prevalent genotype in Brazilian chronically infected patients in São Paulo city.⁶ HBV genotype A was the most prevalent genotype, while genotypes C, D and F were also found among HBV-infected patients in the Southeast of Brazil.¹⁹⁹ Subgenotypes A1, A2, genotype D, mixed genotypes A1 and E were observed in an isolated Afro-Brazilian community.¹³⁸ Genotype A (subgenotype A1) was most prevalent genotype circulating in Brazil with low prevalence of genotypes F and D were the most common genotype in the South and Central regions.¹³² High proportion of subgroup A (genotype A) was found among Brazilian isolates of Hepatitis B virus.¹³ In two Brazilian hemodialysis centers, we observed following subgenotypes of HBV: In hemodialysis unit A (Rio de Janeiro), subgenotypes: A1, A2, A3, D3 and D4 were observed. Pattern A2 was observed in the majority in the hemodialysis patients. In hemodialysis unit B (state of São Paulo), all patients who seroconverted were infected with HBV isolates of genotype D. Coinfection with strain A1 was also detected.⁵⁵

Genotype D was the only genotype in the different clinical forms of HBV infection in Iranian patients with HCC.⁴ Genotype D had been recognized as the only type of genotype found in different clinical forms of HBV infections, including cirrhosis, among the residents of Southwest Iran.¹³⁶ Genotype D was the only genotype found in HBV patients in Iran.¹⁰

HBV subgenotypes A1, A2, B1, B2, C1, C2, D2, and genotype H were detected in Japan.⁷⁸ Genotype C was the most frequent genotype followed by genotypes B, D and A in children in Japan.⁸⁵ A significant number of patients from Western Japan were found to be infected with HBV genotype D and coinfecting with genotype C.¹³⁴ Genotype B was prevalent genotype followed by genotype C in Japan.⁸⁶

HBV genotypes A to G were found, with genotypes A and C the most common in different regions of the United States.⁵⁰ Genotypes A, B, C, D and F were observed from volunteer blood donors from two large, regional blood centers in the United States.¹³⁷

Genotype D was the most prevalent genotype followed by genotype A in chronically infected patients from Spain.²²

The viral genotypes D/ayw2, D/ayw3 and A/adw2 were found with an additional participation of the genotypes D/ayw4, F/adw4q-, A/ayw1 and D/adw3. Strains from genotypes B and C were found exclusively among Chinese immigrants. Genotype E strains were found in immigrants from Central Africa and in native of Spain.⁶² Genotype A was prevalent followed by genotype D, genotype F, genotype C, genotypes A-G coinfection, genotypes A-D, genotypes D-G coinfection, genotypes A-C coinfection and genotypes A-D-G coinfection in Spanish hepatitis B carriers.¹⁶³

Genotype D was observed in Turkish population.¹⁷⁶ The predominant genotype in CHB patients in Turkey was genotype D.¹⁹² Genotype D was observed in the south of Turkey.¹⁷⁵ Genotype D was observed in chronic hepatitis B in Turkish patients.³⁰

Genotype D with genotypes A and F were observed among patients under lamivudine treatment in the City of Ribeirão Preto, State of São Paulo.⁷⁶ Genotype B and C were found among a cohort of Canadian mothers and infants.¹⁸¹ An unusual HBV variant, assigned provisionally to genotype I, was recently reported in the patient, who had immigrated to Canada from Vietnam.¹⁶⁰ HBV genotype distribution was genotypes A, D, G, E, F and C with multiple HBV genotypes in HIV-infected patients with chronic hepatitis B in Europe.¹⁸⁶ A new isolate of HBV from the Philippines possibly representing a new subgenotype C6 was observed along with genotypes B, C5, D and A1 and double infection with genotypes B and D from asymptomatic HBV carriers from the Philippines.³⁴ Genotypes A, B and C were observed among lamivudine-resistant HBV strains of South Africa.¹⁷⁴ Subgenotypes A2, B4, C2, D1, D2, D3 and D4 and genotype E were found in acute HBV isolates from England, 1997-2001.¹⁸³ HBV genotype D appeared to be the only circulating genotype in Jordanian patients.¹³⁰ Genotype F was the most prevalent genotype along with genotypes A, B, C and D in chronic HBV carriers in Santiago, Chile.²⁰⁴ Genotype D was prevalent genotype followed by genotype A in Romania.⁴⁹ Genotype E was found to be prevalent genotype followed by subgenotype A1 and genotype D in the Central African Republic.²⁴ HBV genotype A (subgenotypes A1 and A2) was the most predominant genotype along with genotypes D and E in Kenya.¹⁴² Genotype D was the only genotype found in Mongolia.⁶³ HBV genotypes, A and D, were found in Serbia, with genotype D and subgenotype D3 being prevalent genotype.¹⁰⁶ HBV infections in pediatric cancer patients were attributed predominantly to viral genotypes D and B. In addition, there was a relatively high prevalence of mixed A/D genotype infections in Egyptian pediatric cancer patients with acute and chronic active HBV infection.²²⁰

Genotypes A, B, C, D, E and F were identified from acute HBV infections in the Netherlands in 2004 and genotype A was predominant in the Netherlands, especially among men having sex with men.²⁰³ Among two different ethnic populations from the Solomon Islands, the major Melanesian genotype was genotype C, whereas the major Micronesian genotype was genotype D. Subgenotypes C3 and D4 were observed and the genotype D was related closely to those from Papua New Guinea.²⁰² Genotype D was the predominant genotype followed by genotype E, genotype A, genotype C in Saudi Arabia.¹ HBV genotype H was highly predominant in HBV isolates of Mexico followed by genotypes G, A and D.⁸ Genotype A was predominant genotype followed by genotype D and mixed genotype A/D in the area of Central Poland.¹⁸⁴ Genotype A was prevalent genotype followed by genotype D in European children.²¹² HBV genotype A was the most frequent genotype followed by rare genotype G in HIV/HBV-coinfected patients in France.¹⁰⁴ HBV genotype D, subgenotype D1 was found among hepatitis B-infected patients from Afghanistan.⁹ Absolute domination of genotype D (subtypes ayw2, ayw3 and adw2) was revealed among HBV isolates among indigenous population of Yamal-Nenets Autonomous Region (YNAR), Russia.¹²⁹ Genotypes A and D were the predominant genotypes in Belgian patients with chronic HBV infection.¹³³ Genotypes C, B and D of HBV were observed in Malaysia.¹⁵⁷ HBV genotype distribution among the multiethnic carriers in Hawaii was genotypes A, B and C.¹⁶⁸ Genotype C was prevalent genotype followed by genotypes A and B on Jeju Island in Korea.⁴⁶ The most common viral genotype was genotype D of HBV among children in Moscow, Russia.² Genotypes A, D and A/D were observed in patients of European origin.⁷⁴ Genotype B was main genotype observed in Surabaya, Indonesia.¹²¹ Genotype C was the most common genotype encountered in HCC patients in Korea, China, Vietnam and Spain.⁵⁹ Genotypes A and D were observed in Uzbekistan.⁹⁷ Samples from Southeast Asia were predominantly genotype B/subtype ayw1 and genotype C/adr; samples from the former Soviet Union and Eastern Europe were mostly genotype D/ayw2 and genotype D/ayw3; samples from east Africa were mainly genotype A/adw2 and genotype D/ayw2; and samples from injection drug users were mostly genotype D/ayw3 and genotype A/adw2 in refugees and injection drug users in the United States.¹⁹³ Genotype C and an aberrant genotype [recombination between genotype C and a putative new genotype (or possibly a subgroup of genotype A)] were observed from Vietnam.⁷⁷

DISTRIBUTION OF HBV GENOTYPES AND SUBGENOTYPES IN INDIA

Recently, Arankalle et al¹¹ reported genotype I from the Idu Mishmi primitive tribe of Northeast India. Chandra et al⁴⁰ observed subgenotypes D1, D2, D3 and D5 in the HBV-infected persons from the state of West Bengal, India. Datta et al⁵⁷ found HBV genotypes A (Aa/A1), C (Cs/C1) and D (D1, D2, D3, D5) in the Eastern Indian population. In addition to genotype D and genotype A, genotype C was also present among the voluntary blood donors from Eastern India, most frequently in the 18 to 25 years age group.²⁶ The predominant genotype was genotype A followed by genotypes C and D in Arunachal Pradesh.²⁸ A novel subgenotype of D, designated as D5, had been identified from Eastern India.^{21,172} The predominant genotypes D, A and C were detected among HBV carriers in Kolkata, Eastern India.²⁰ In the eastern part of India, three different HBV genotypes (genotypes A, C and D) were observed.^{20,21} Subgenotypes A1, C1, D1, and D3 were prevalent in the eastern part of India as observed by Banerjee et al.²⁰ Genotype D was the predominant genotype followed by genotypes C and genotype A from chronic carriers of the virus from Kolkata, Eastern India.¹⁹

In a study from New Delhi, HBV/D was the predominant genotype associated with HCC cases seen in India followed by HBV/A.¹⁵ Genotype D was the predominant genotype found in HBV-related liver diseases in North Indian patients.¹⁷⁷ In a study from New Delhi, the most common genotype was D followed by A and C among Indian patients.¹²³ In a study from New Delhi, Kumar et al¹⁰² found subgenotypes A1, D1, D2 and D5 and genotype G in family contacts of HBV infected patients with occult hepatitis B virus infection. Singh et al¹⁸² observed genotype E first time along with genotype D (subgenotype D1), A (subgenotype A1) in North Indian population. In a study from New Delhi, Chauhan et al,⁴³ identified and characterized recombinant A and D genotypes of HBV in Indian chronic HBV isolates. Kar et al⁹⁶ observed genotype D as predominant genotype in both wild and mutant forms of the HBV among chronic liver disease patients from New Delhi. In a study from New Delhi, Chauhan et al⁴² observed HBV genotypes A, D and B/C in India. HBV genotypes A and D were found to be prevalent in patients with HBV related acute and fulminant hepatitis from New Delhi, India.⁴¹ In the Northern India, genotypes A and D were found to be equally prevalent.^{196,101}

A study of HBV isolates from the Onges, Nicobarese and Great Andamanese indicated a predominance of genotype D. In contrast, genotype C predominated among the Jarawas, with isolates similar to strains from Southeast

Asian countries.¹⁴¹ The predominance of HBV/C1/Cs and in addition, acquired HBV/D2 among Karens, the 'old settlers' of Andaman and Nicobar Islands, India.⁵³ The prevalence of HBV genotype C and D was prevalent among other non-Jarawa tribes of the Andaman and Nicobar Islands, India.¹⁴⁰ Genotype D1 was most prevalent in a South Indian population.¹⁹⁷ Vivekanandan et al,²⁰⁶ observed genotypes D, A and C among patients with CHBV in Southern India. Genotypes D and A were observed and predominance of genotype D in primitive tribes of the Andaman and Nicobar islands, India.¹²

Gandhe et al⁷⁰ observed genotype D and genotype A in Western India and genotype D was the predominant genotype circulating in Western India.

INFLUENCE OF HBV GENOTYPE/SUBGENOTYPE ON THE DISEASE PROGRESSION

Genotype F was the prevalent genotype among the acute symptomatic infections in Buenos Aires city, Argentina and genotype F showed a tendency to cause an adverse disease outcome among the chronic cases.¹⁶⁶ Certain HBV genotypes and subgenotypes C, B2-5 and F1 appeared to be associated with a higher risk of developing HCC, and others genotypes B1, B6, and A2 appeared to be associated with a lower risk of complications of HBV.¹³¹ Patients with genotype C were more likely to have HCC. Waitlist mortality was highest among patients with genotype D, while posttransplant mortality was highest among patients with genotype C.⁶⁹ In China, HBV coinfections with two or three genotypes were associated with higher viral load and more severe course of the disease. HBV B2 infection was related to HCC recurrence and HBV C2 was found more in HCC patients.²¹⁶ In a study from Taiwan, HBV genotype C was associated with increased risk of HCC development.¹¹² HBV genotype C was reported to be associated with increased risk of HCC development.⁹² A prospective study from Hong Kong showed that the highest risk of developing HCC was in persons infected with HBV genotype C2 (Ce) and the next highest in C1 (Cs) than those infected with genotype B (presumably Ba).³⁷ HBV subgenotype C2 was more prone to causing chronic HBV infection than was HBV subgenotype B2 in Shanghai, China.²²² In Pakistan, genotype A was found to be more strongly associated with severe liver disease.¹⁷ A study from Alaska showed that genotype D was significantly associated with HBV-associated vasculitis (polyarteritis nodosa) in comparison with genotypes A2, B6, C2 and F1.⁸² In HBV-infected patients from Northern Vietnam, genotype C had a higher HBV-DNA level than genotype B and genotype C was associated with progressive severe liver diseases.²⁰⁰

Subgenotypes of HBV/C may not have a clinical impact on the disease progression of chronic hepatitis B in Taiwan.²⁰¹ In a study from Germany, children with genotype D showed a significantly higher viral load as compared with children with genotype A.¹⁵⁸ In Japan, persistence of HBV was associated with Ae, whereas fulminant hepatitis was associated with Bj.¹⁶¹ In a study from Vietnam, genotype A was more frequent in asymptomatic patients as compared with symptomatic patients. Genotype C was more frequent in patients with HCC. Genotype mixtures were more frequently encountered in patients with chronic hepatitis in comparison to patients with acute hepatitis B, liver cirrhosis and HCC. Viral loads in patients infected with genotype mixtures were significantly higher in comparison to patients with a single genotype.¹⁹⁸ Compared with genotype B, genotype C was associated with the development of more severe liver damage in Guizhou, China.⁵⁸ In a study from Taiwan, patients infected with genotype C had a lower remission rate and more adverse outcomes than those with genotype B of HBV.¹⁸⁸ In a study from Taiwan, genotype C of HBV infection was associated with a higher risk of reactivation of hepatitis B and progression to cirrhosis than genotype B.⁴⁸ In a study from Taiwan, compared with genotype C, genotype B was associated with earlier HBeAg seroconversion, slower progression to cirrhosis and less frequent development of HCC.⁸⁸ In a study from China, HBV genotypes B and C were associated with different patterns of end-stage liver diseases that required transplantation and genotype C may carry a greater risk and severity of recurrence due to lamivudine-resistant mutants.¹¹⁸ In Northern India, genotype A was more often associated with ALT elevation, HBeAg positivity, absence of anti-HBe and among aged 25 years and above, cirrhosis of liver, than genotype D.¹⁰¹ A 4.5-fold increased risk of HCC was found in those infected with genotype A *versus* those infected with other HBV genotypes in a case-control study of HBsAg-positive Africans.⁹⁸ There is increasing evidence that patients infected with genotype C had more severe outcome of chronic liver disease than those infected with genotype B. Patients infected with genotype B appeared to seroconvert earlier than those infected with genotype C.⁷ Genotype A1 had been associated with very high rates of HCC in sub-Saharan Africa.⁹⁸⁻¹⁰⁰ Patients with HCC with genotype C had a greater tumor recurrence rate after curative resection of HCC compared with those with genotype B.⁴⁵ In Japan, genotype C was associated with chronic liver disease and genotype D was related to asymptomatic carriers with earlier HBeAg seroconversion.⁶¹ In Taiwan, genotype C was associated with more severe liver disease including cirrhosis and HCC, whereas genotype B was associated with

the development of HCC in young noncirrhotic patients.⁹⁴ In a study from China, disease activity was greater in patients infected by HBV genotype C than in those infected by HBV genotype B in the HBeAg-positive phase but not after HBeAg seroconversion.³⁹ In a study from Taiwan, genotype C was associated with more severe liver diseases than the B variant.¹⁰⁸ In a study from the Okinawa islands, HBeAg was cleared from sera more frequently and earlier in patients with genotype B compared with those with genotype C, and development of cirrhosis occurred less frequently in patients with genotype B compared with those with genotype C.¹⁴⁵ In Changzhou area of China, genotype C was associated with the development of severe liver disease.²⁰⁹ In a study from Spain that included both interferon-treated and untreated patients, those infected with genotype F were reported to have lower cumulative probability of sustained biochemical remission and HBV DNA loss and a significantly higher cumulative liver-related death rate than those infected with genotype D or A.¹⁶⁹ A study from India reported that genotype D was associated with more severe liver disease and HCC in younger patients than genotype A.¹⁹⁶ In Taiwan, genotype C was associated with more severe liver disease and genotype B was associated with the development of HCC in young noncirrhotic patients. In contrast, genotype B had a relatively good prognosis in Japan and China and was rarely associated with the development of HCC. Similarly, genotype D was associated with more severe liver disease than genotype A in India and may predict occurrence of HCC in young patients.⁸⁹ In Taiwan, genotype B was reported to enhance the development of HCC in hosts of younger ages,⁹¹ in striking contrast to genotype B in Japan.¹⁵⁹

HBV GENOTYPE AND ANTIVIRAL THERAPY

In a study from Philippines, HBV genotype A has an advantage in the response to pegylated interferon.³ Genotype A of HBV responds best to peginterferon but HBV genotype has no predictive value for nucleos(t)ide analogue treatment.²¹³ Compared with HBV genotype C, genotype B shows an earlier biochemical resistance to lamivudine.⁸⁰ The best candidates for a sustained response to PEG-IFN- α are genotype A patients with high levels of ALT or low levels of HBV DNA, and genotypes B and C patients who have both high levels of ALT and low HBV DNA. Genotype D patients have a low chance of sustained response.³² HBV genotypes A and B are more sensitive to interferon treatment than genotypes D and C, respectively.³³ HBV genotypes E, F, and H appear to be sensitive to IFN α . Lower rates of response to IFN- α in patients with HBV genotype G might be related to the frequent occurrence

of double infection.⁶⁵ HBeAg-positive patients with genotype A have higher rates of HBeAg and HBsAg clearance, whereas HBeAg-negative patients with genotype D have the lowest rate of response to interferon therapy.¹⁶⁵ The best response to IFN α and PEG-IFN α is obtained in patients with elevated transaminase levels, moderate viral load and HBV genotypes A and B.⁷³ In Chinese Han CHB patients who are HBeAg-positive, HBV genotype B shows a better virological response to ADV therapy (Adefovir dipivoxil therapy) than does genotype C.²²¹ Recent studies suggested that responses to standard interferon treatment in patients with genotypes A or B are better than those with genotype C or D.¹¹⁶ The sustained response rate to peginterferon α (PEG-IFN) is significantly higher in genotype B than in genotype C patients.¹⁷⁹ Pegylated interferon therapy is often a better choice for young to middle-aged patients with genotypes A and B because of the higher rate of HBeAg seroconversion and a greater chance for HBsAg seroconversion in both HBeAg-positive and negative patients as compared to nucleoside analogs.²²⁶ Lamivudine resistance mutations are more frequent in HBV genotype A than D.¹⁷⁸ As to the treatment of chronic hepatitis B, patients with high HBV DNA level and genotype C or D infection are shown to have a worse response to interferon therapy.⁹⁵ In a study from China, the response to IFN α in patients with genotype B is markedly better than in those with genotypes C and D, and the complete response to IFN α is only observed in genotype B.¹²² In a study from Japan, genotype C is considered more refractory to antiviral therapies than genotypes A and B.¹³⁵ The response rate to antiviral therapy in Chinese patients is higher in genotype B than genotype C patients on interferon treatment, but no difference was observed on nucleoside/nucleotide analog treatment.²¹⁰ Alpha-interferon treatment for HBV genotype B CHB patients is more effective than that for the genotype C patients.²²⁵ HBV genotypes D and C are associated with a lower rate of favorable response to α -interferon and pegylated-interferon α -2b therapy than genotypes A and B. The rate of resistance to lamivudine was higher in patients with genotype A infection than in patients infected by genotype D, whereas no difference in the risk of lamivudine resistance is found between patients with genotype B and patients with genotype C.¹⁶² During the peginterferon α -2a and lamivudine monotherapy, patients with genotype B or C have a higher chance of response than genotype D-infected patients.²⁷ A study in Germany suggests that the rate of resistance to lamivudine is higher in patients with HBV genotype A infection than in patients with genotype D infection.⁶⁴ A better sustained response to conventional interferon is found in patients with genotype B than those

with C, and in patients with genotype A than those with D.¹¹³ A study from Germany indicates that HBV genotypes A and D are important and independent predictors of IFN responsiveness in chronic hepatitis B.⁶⁵ HBV genotype B is associated with a higher rate of lamivudine-induced HBV DNA clearance and lower rate of lamivudine-induced YMDD mutation compared with genotype C.²²⁴ HBV genotype C is associated with a lower response rate to interferon therapy compared with genotype B. In addition, genotype B seems to have a better virological response to lamivudine as compared with genotype C, but both genotypes have a similar risk in the development of lamivudine resistance.⁹⁴ HBV genotype B is associated with a higher rate of IFN-induced HBeAg clearance compared with genotype C.²⁰⁷ HBV genotypes C and D are associated with a lower response rate to interferon therapy compared with genotypes B and A.⁹³ HBV genotype C, compared with genotype B, is associated with a higher frequency of core promoter mutation, and a lower response rate to interferon alfa therapy.⁹⁰

CONCLUSIONS AND FUTURE PERSPECTIVES

HBV is the smallest known DNA virus infecting mankind and despite the availability of a vaccine its infection is responsible for nearly two millions deaths worldwide. So, HBV infection remains a global health problem and a public health threat in the present era. India is a prosperous country and has peculiar geographical presence which is responsible for evasion of this land by traders and invaders in past and resulted in gene influx due to invasion and/or anthropological migrations in the past. This results in the introduction of new genotypes/subgenotypes of HBV in India. New anthropological migration from Bangladesh and Tibet had made this problem more dangerous due to presence of B/C and C/D recombinant genotypes in their population, respectively. The presence of nearly all genotypes/subgenotypes in our Indian population is an alarming situation. The emergence of new genotypes/subgenotypes has immense importance in determining the clinical outcome, efficacy of vaccination and therefore strict surveillance of these variants is extremely important. There are enough evidences in literature which demonstrated the influence of different genotypes on disease progression, severity and response to different therapies. Presence of nearly all subgenotypes in same ethnic group may provide an opportunity to study the different pathogenic behavior of different subgenotypes. It will further keep in understanding the mechanistic difference between different subgenotypes in relation to disease progression. In last decade, evidences are accumulating with fast speed that

human alleles are also related to the disease outcomes. Some alleles show resistant property, while other shows more susceptible property regarding the pathogenicity of HBV infection. So, study of viral factors (genotypes/subgenotypes) and their relationship with human alleles may further lessen the burden of HBV infection in next generation. So, overall a multicohort studies at both national and international level and implication of genetic and clinical data may help us in understanding the immunopathogenesis of different genotypes/subgenotypes. Hope that the present review will advance the understanding of changing molecular epidemiology of HBV and will also help in formulation of effective preventive measures.

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