

A Review on Hepatitis B Virus, its Genotypes and Risk Factors

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Abstract: Hepatitis B virus (HBV) is a pathogen causing infectious diseases globally and is a circular partially double-stranded DNA pathogen with a diameter of 40-42 nm. Worldwide about 2 billion individuals are infected from this pathogen and 350 million individuals are chronically infected from HBV. It is 10th progressive reason of death in whole world. HBV can be transmitted vertically and horizontally. Vertically it can be transmitted from infected mother to child and horizontally by blood transfusion. Study revealed that 37% and 36% persons were infected by surgical operations and dental procedures respectively, 24% by blood transfusion, 2% by intravenous drug use and 1% by infected body fluids and through sexual contacts. Pathogen transmitted by ear and nose piercing, tattooing due to use of infected instruments, needle stick injuries and by sharing tooth brushes are main factors of virus transmission. HBV have eight genotypes (A-H) and many sub-genotypes, which may vary from area to area. Recently 2 more genotypes (I and J) were discovered. The prevalence of various HBV genotypes is variable in area to area and race to race but Genotype C and D are most common in Pakistan. Prevention is better to overcome the HBV infection. Launching of vaccination programs will help to minimize the chronic hepatitis B (CHB) burden. Awareness programs in backward areas regarding the risk factors of HBV may be useful in reducing this disease.

Key words: Virus • Genotypes • Risk Factors • Blood Transfusion • Prevalence

INTRODUCTION

History and Structure of Hepatitis B Virus: Hepatitis B virus (HBV) is the common disease causing virus around the globe. HBV is circular, partially double-shelled and double-stranded DNA pathogen with a diameter of 40-42 nm. Pathogen was discovered in 1967 by Dr. Blumberg [1]. HBV belongs to genus *Orthohepadnavirus* and family *Hepadnaviridae*. Inside the nucleocapsid, DNA is present covered by circular envelope. The whole virion is called as Dane particle. Including core and surface proteins, the HBV genome covers the DNA polymerase which acts like a reverse transcriptase [2]. At endoplasmic reticulum, a complex transmembrane fold of L, M and S shape proteins are present, which are known as envelope proteins (Fig. 1). This makes disulphide-linked hetero and homodimers [3].

Prevalence of Hepatitis B Virus: About 2 billion individuals are infected from HBV in whole world and greater than 350 million individuals are infected from severe or chronic HBV. Globally small numbers of children

are infected from chronic HBV [4]. HBV is main source of hepatic decompensation which may leads toward cirrhosis and hepatocellular carcinoma [5]. In Asia and Western Pacific about 75% of individuals are chronic carriers [6]. Around 3% population of Pakistan is infected from HBV [7]. Symptoms of HBV include nausea, fatigue, anorexia, low temperature and joint pain [8].

Clinical Diagnostic Test for HBV Genotypes:

Genotypes of HBV can be detected by many procedures such as line probe assay, ligase chain reaction assay, restriction fragment length polymorphism analysis, polymerase chain reaction (PCR) using type specific analysis, for genotype specific epitopes enzyme linked immunosorbant assay (ELISA) and direct sequencing are used. Some serological markers are also used for diagnosis of HBV including hepatitis B core antigen (HBcAg), hepatitis B surface antigen (HBsAg), hepatitis Be antigen (HBeAg) and enzyme immunoassay (EIA) [9, 10] (Table 1). Various procedures and serological markers to detect the HBV in various populations of Pakistan are represented (Table 1).

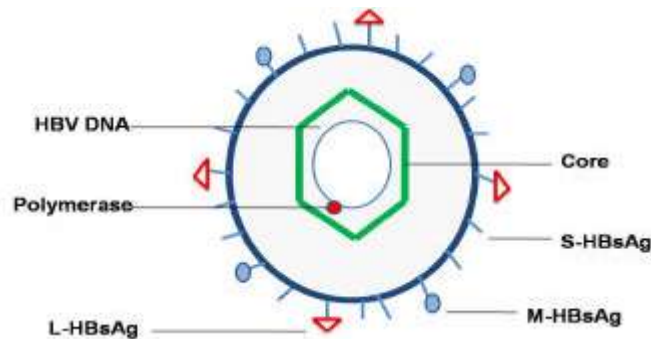


Fig. 1: Structure of HBV showing different structural proteins [3].

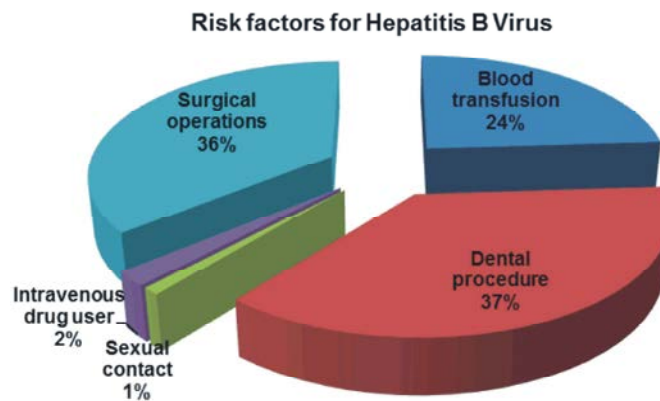


Fig. 2: Frequency of risk factors of Hepatitis B Virus based on study of Sureshkumar *et al.* [20].

Table 1: Frequency of HBV, serological markers and its diagnostic procedures adopted in different areas of Pakistan

Population type	Area	Procedure and HBV serological markers	Total population size/ and % of +ve samples	Ref.
Prisoners	Bahawalpur	ICT and ELISA/ HBsAg	2086/ 5.6%	[11]
	Karachi	ELISA/ HBsAg and DNA	365/ 5.9%	[12]
Common population	Larkana	ELISA/ HBsAg and DNA	200/ 4.8%	[13]
	Karachi	ICT, ELISA and PCR/ HBsAg and DNA	3820/ 4.5%	[14]
Blood donors	Peshawar and KPK	MEIA/ HBsAg	4000/ 1.9%	[15]
Patients with hepatocellular carcinoma	Rawalpindi	ICT, ELISA/ anti-HBsAg, anti-HBeAg and anti-HBcAg	44/ 25%	[16]
	Hyderabad	ELISA/ HBsAg	200/ 21.0%	[17]

ICT: Immuno-chromatographic test, MEIA: Microparticle enzyme immunoassay.

Risk Factors: HBV was found to be transmitted horizontally i.e. by blood contact as studied in United States of America and Western Europe. Equatorial Africa and Southeast Asia are the most endemic regions where HBV was found to be transmitted vertically, where pathogen was transmitted from infected mother to child [18]. Around 37% and 36% persons were infected by surgical operations and dental procedures respectively (Fig. 2). Blood transfusion was the main transmission route of HBV in 24% individuals. HBV can be transmitted by intravenous drug use (IVDU) (2%), contact with infected body fluids and through sexual contact (1%) [19].

HBV can be transmitted by needle-stick injury reported in hospitals, lab technicians and nurses [20]. A study described that 59 of 255 (23.13%) persons were infected due to needle-stick injury [21]. The pathogen spreads by tattooing, sharing tooth brushes, razor, ear or nose piercing [22, 23]. Another study based on medical students survey concluded that 80/92 (87.0%) surveyor concluded that HBV spreads by blood transfusion, 38/92 (41.3%) argued that the pathogen can be transmitted by breast milk and 40/92 (43.5%) revealed that saliva is the main factor of HBV spread. Around 32/92 (34.8%) students were in view that this pathogen can be

Table 2: Worldwide distribution of HBV genotypes/sub-genotypes

Genotypes/Sub-genotypes	Worldwide distribution	Ref.
A	North America, Southern and East Africa, Western Europe	[30]
A1 and A2	India, Asia, South Africa and Europe, Australia	[31]
B (Ba and Bj)	Southern China, Taiwan, Vietnam, Asians in USA, Japan	[32, 33]
C (C1-C5)	China, Japan, Thailand, Southeast Asia, Australia	[33, 34]
D (D1-D4)	Russia, Middle East, North Africa, Arabs and Indians	[9,35]
E	West and Central Africa	[36]
F (F1)	Central and South America, Alaska,	[37, 38]
G	France and United States	[39]
H	Central America and Amazon region	[40]
I and J	Vietnam and Loas and Ryukyu Islands (Japan)	[41, 42]

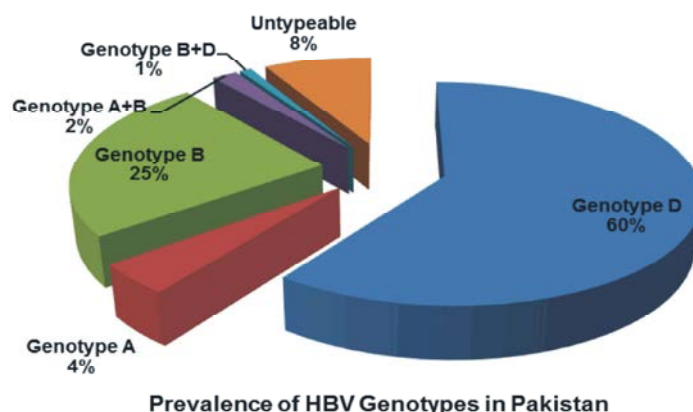


Fig. 3: Prevalence of HBV Genotypes in Pakistan. Figure showing Genotype D as most frequent and Genotype B+D as least frequent in Pakistan. The graph is based on statistics provided by [25].

transmitted by sharing food or drink utensils with infected person [24]. Pathogen can be transmitted through infected instruments. The prevalence of HBV was seen in drivers (5.1%), house maids (24.5%), soldiers and policeman (6.1%). Pathogen can be transmitted by airborne method and smoking [19]. A study performed on IVDU in Pakistan revealed the presence of genotype A in 8.9%, genotype D in 60% and genotype B prevalence in 24.5% infected individuals [25].

Geographic Distribution and Prevalence of HBV Genotypes:

HBV have eight genotypes (A-H) and many sub-genotypes. The newly discovered genotypes are I and J. The prevalence of genotypes is different from region to region due to their geographic and ethnic distribution. HBV have four serotypes consisting of *adw*, *ayw*, *adr* and *ayr* [5] (Table 2). In Northwest Europe, India, Central and South America, A genotype was common. B and C genotypes were prevalent in Southeast Asia and D genotype in Mediterranean countries and South America. E genotype was limited to West Africa and F genotype in Central and South America [25, 26]. According to a study conducted in various provinces of Pakistan, of the total HBV positive cases, 46 samples were

genotype C (41.07%), the most common type investigated. Mixed genotypes were found in 8 (7.14%) infected persons, of which genotype A/D was common in five patients, while genotype C/D was found in two individuals. Four genotypes (A, B, C, D) were detected in a single patient. The prevalence of genotype A was 68% in Sindh Province. In KP, 68.96% individuals were infected from genotype C while both genotypes B and C were more prevalent in Punjab [27]. Studies reported that C genotype is most prevalent with the frequency rate of 27.66% in Pakistan as compared to other genotypes. However the studies conducted in past revealed that D genotype showed best response to interferon therapy as compared to A and B genotypes [28, 29].

A study was conducted in Pakistan on 110 (15.9%) HBV positive cases (male and females). Of the 110 cases, 66 (60%) patients were related to genotype D, 5 samples (4.5%) were genotype A and genotype B related samples were 27 (24.5%). Multiple genotypes were diagnosed in 3 (2.7%) including 1 (0.9%) with genotype B+D and 2 (1.9%) with genotype A+B, while remaining 9 (8.2%) samples were unknown, i.e. were not from any type (Fig. 3). This concluded that genotype D was most prevalent in Pakistan and B, C genotypes were more prevalent in

Asian countries [25, 43]. Another study demonstrated that the most prevalent genotypes in China were B and C with percentage of 41% and 53%, however A and D genotypes were prevalent in few provinces of China [44].

Treatments: HBV is treated by several antiviral drugs and therapies consisting of lamivudine, telbivudine, interferon alfa-2b, tenofovir peginterferon alfa-2a and entecavir [45, 46]. The reported HBV genotypes are linked with response to interferon. Studies indicated that A and B genotypes have greater rate of HBeAg seroconversion followed by C, D and E genotypes [47, 48]. The most popular therapy is peginterferon alfa-2b used for the clearance of HBsAg in patients who were infected with a genotype [49]. Another study revealed that B genotypes showed best response to lamivudine as compared to C genotype [50]. The latest methods for HBV genotypes detection are genotype sequencing, RFLP, RFMP, Multiplex PCR, Reverse dot plot, Serotyping, INNO-Lipa and Real-time PCR [51]. The study evaluated that genotypes showed different response to antiviral therapy and interferon in chronically HBV infected patients. B genotype showed good response to interferon than C genotype. Many procedures were used for HBV genotyping. For the diagnosis of lamivudine resistance, nucleotide sequencing of PCR product was used on daily bases [47].

A study was conducted on 126 HBV infected samples. HBV genotyping was done by real-time PCR, oligonucleotide chip and sequencing and result were compared. Fully concordant results were achieved in 117 samples with the percentage of 93% by the three techniques. B and C genotype was diagnosed by sequencing and both genotypes were diagnosed by real-time PCR and oligonucleotide chip in the mixture of 9 samples. Both genotypes B and C was diagnosed by real-time PCR and oligonucleotide chip in the mixture of 9, 41 and 76 samples with the percentage of 7%, 33% and 60% correspondingly. Other genotypes were not diagnosed in this study. So mixed genotypes in samples were diagnosed by real-time PCR and oligonucleotide chip [52]. Another study reported that A genotype patients showed best response than D and C genotype and B genotype showed good response than C genotype [53].

CONCLUSION

The genotypes of HBV vary from region to region and its prevalence is increasing day by day. It is recommended to aware the people about risk factors of

HBV regarding blood transfusion, nose and ear piercing, use of sterilized needles in health care centers. Different program and campaigns should be launched to control the infection of HBV. HBV vaccination should be increased to reduce the frequency of HBV infection. So HBV can be curable at early stages and can be treated by vaccines. Introducing new antiviral drugs and treatments can play a significant role in reducing HBV infection.

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