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Review Article

Genotypes Variation and Molecular Epidemiology of the Hepatitis B Virus Chronic Liver Infection in The Local Population of Pakistan: An Overview of The Recent Literature

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ABSTRACT

Hepatitis is defined as an enlargement of the liver. Viral hepatitis is the word used for the group of liver ailments generated by viral infections. There are approximately 350 million people worldwide who have chronic hepatitis B virus (HBV) infection. HBV is estimated to kill 563,000 people each year and cause a high rate of infection. The Hepatitis B DNA virus comprises of a 3.2 kb relaxed-spherical DNA molecule. Of the total eight genotypes of HBV, genotype D is the most common, with an actual incidence rate of 63.71%, followed by genotype A at 10%, according to ten distinct studies conducted in diverse parts of Pakistan. Symptoms may take up to six months to emerge after exposure. Early signs and symptoms of HBV infection are lethargy, nausea, poor appetite, vomiting, pyrexia, headache, muscle pain, joint pain, gastrointestinal disturbances, dark urine, and jaundice. Pakistan is one of the worst affected countries, with over 40 million Pakistanis infected with HBV. This article provides an overview of the epidemiology and natural history of HBV infection and its diagnosis and treatment.

INTRODUCTION

Hepatitis is a word defined as an enlargement of the liver. Viral hepatitis is the term used for the group of liver ailments [1]. These liver ailments are caused by viral contamination of the liver cells. It is caused by persistent viral infections, with five different viruses commonly spreading disease within hepatocytes tortuously. All five viruses are called "human hepatitis viruses"(A-E)[2]. These pathogens are a class of dissimilar viral families and are the source of liver morbidity with different features. These viruses also have different epidemiological relationships, communication pathways, and geological spread [3]. Hepatitis A and E viruses cause diseases that are spread through polluted water, whereas hepatitis B, hepatitis C, and hepatitis D viruses cause illnesses that are conveyed through blood [4]. HBV is a DNA virus, that was first detected in an Australian aborigine in 1965 by the detection of its antigen [5], which is now designated as surface antigen, as per Blumberg and colleagues [6]. In 1970, Dane

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and colleagues used an electron microscope to examine viral particles. In consonance with the International Committee on Taxonomy of Viruses (ICTV), this virus is owned by the Hepadnaviridae family's Ortho-hepa-dna virus genus. This pathogen is also associated with the subfamily Spumaretrovirinae, which is part of the Retroviridae family [7]. It is also the only known animal virus with a DNA genome that can be cloned by reverse transcription of a viral RNA intermediate [8]. HBV is among the main causes of hepatocellular carcinoma and cirrhosis-related end-stage liver disease. According to the World Health Organization (WHO), there are approximately 350 million people worldwide who have chronic HBV infection [9]. Hepatitis B is estimated to kill 563,000 people each year and cause a high rate of infection. Pakistan is in the middle of the most terrible afflicted nations [10]. The incidence of HBV infection is reported as being around 4-12%. In small scale investigations, a higher incidence of HBV has been reported in several locations of Pakistan. The higher occurrence is described by numerous factors involving the transfusion of vulnerable blood or blood products [11], the handling of germfree syringes in the common practice [12], nose or ear piercing with the germless needles and persistent visits to hairdresser [13]. Germless syringes used by intravenous drug users are a remarkable etiological element of HBV infection worldwide [14]. Pakistan is the nation with the highest count of intermuscular inoculations administered. Perpendicular diffusion seems to help more than parallel diffusion in the occurrence of persistent HBV infection in this nation. Safe intimacy contributes to a minor number of cases as compared to advanced countries [15]. HBV was separated by Blumberg in 1965 and it is a DNA virus as compared to hepatitis C virus (HCV), which is a hepatotoxic viral infection first cloned in 1989 [16]. Co-infection of HCV and HBV is very common and is linked with dangerous complications. Numerous studies were conducted in various locations to determine the prevalence of HBV in Pakistan [17]. A survey-based study was conducted by the Pakistan Medical Research Council all over the country for the span of 10 months (2007–2008). In this study, it is reported that the ubiquity of HBV is 2.5% [18]. The immediacy of HBV at the provincial level was also observed in prior studies. HBV was found in 9.3% of Baluchistan's population; meanwhile, it was 2.3% in Sindh, 2.4% in Punjab, and 1.31% in Khyber Pakhtunkhwa, respectively [19]. The current review examines the epidemiology of hepatitis B virus infection in Pakistan. The purpose of this review was to conduct a literature review to evaluate the current pervasiveness of hepatitis B infection in Pakistan as well as related risk factors.

Morphology: At least three varieties of HBV nanoparticles have been reported in the serum of infected individuals: Circular structures with a diameter of 42 nm. Dane particles are another name for them [20]. It's a contagious virion with a lipid membrane and three viral surface antigens (HBs): large (L-HBs), middle (M-HBs), and small (S-HBs).Hepatitis B core protein (HBc), viral polymerase (Pol), and infectious genomic DNA are all contained within a nucleocapsid enveloped by these proteins. HBV evolves in host cells by combining viral proteins with components generated by the host [21]. Filament structures of varying lengths with a diameter of 22 nm [22]. They are considerably more prominent in the patient's serum, which is made up of non-infectious subviral particles (SVPs) that lack the nucleocapsid [23]. Non-infectious particles are now recognized to be occasioned by infection in the formation of encapsulated particles that lack a viral genome [24]. They include viral RNA as well as naked nucleocapsids, which are nanoparticles without an envelope [25]. The HBV genomic DNA is a 3.2 kb relaxed-spherical DNA (rcDNA) molecule with a complete negative strand and an incomplete positive strand [26].The negative DNA strand is 3.2 kilobases long, while the positive strand is between 1.1 and 2.6 kilobases long [27].The incomplete positive-strand DNA of HBV makes it easy to distinguish cDNA from other HBV intermediates. The components of the HBV virion are depicted in Figure 1.

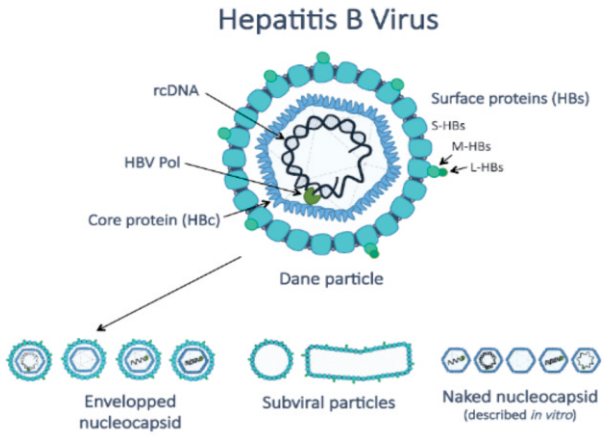

Figure 1: Proteins and structural components of the hepatitis B virus

HBV Genotypes: Worldwide dispersion of HBV genotypes: Each of the eight genotypes (A–H) has a separate geographic origin. Genotypes A and D are the most common in Africa, Europe, and India. Genotypes B and C are found in Asia. The genotype E is found only in West Africa. Only South and Central America are home to genotype F. Although genotype G and H strains from Central and South America, as well as southern Europe, been have found to have a less clear distribution. Perhaps two new genotypes have been discovered. Genotype I appear to be a hybrid between genotypes A, C, and G, and is

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observed in Vietnam, Laos, and Eastern India [28].

Distribution of HBV genotypes in Pakistan: According to ten distinct studies conducted in diverse parts of Pakistan, the generally recognized HBV genotype in Pakistan is genotype D, with an actual incidence rate of 63.71%, followed by genotype A at 10%. The prevalence rates of genotypes C and B are 7.5% and 5.3%, respectively. According to a recent analysis, the most common genotype in the Pakistani population with their prevalence as C (27.7%), B (18%), A (14.3%), D (13%), F (1.3%) and E (0.7%). Another study reported that genotype D is the predominant genotype in all regions of Pakistan with an overall prevalence of about 71 %. Similarly, prior studies have already shown that genotype D has a more serious illness that is less responsive to treatment and has higher HBV DNA levels as compared to genotype A and B.

Epidemiology: Hepatitis B epidemics vary by region, with demographic prevalence, age, route of transmission, and likelihood of progression to chronic disease all interconnected [29]. HBV infects 2 billion individuals worldwide, with more than 350 million suffering from severe illness. Cirrhosis and hepatocellular cancer are caused by HBV and account for 500,000 to 1,000,000 fatalities worldwide each year. In high-pervasiveness areas like Central Asian republics, Southeast Asia, Sub-Saharan Africa, and the Amazon basin, the HBV carrier prevalence is over 8%. In low-pervasiveness areas like the United States, Northern Europe, Australia, and portions of South America, HBsAg prevalence is less than 2%. HBV has infected around 33% of the world's population, with 400 million people suffering from the unending illness. 75% of them live in Asia and the Western Pacific. Hepatitis B prevalence fluctuates all around the world, from high (> 8%) in Africa, Asia, and the Western Pacific to low (2%) in Western Europe, North America, and Australia. The situation is terrible in Asia, Southern Africa, Latin America, and Europe. In 2015, the Sustainable Development Goals included the eradication of hepatitis by 2030. In 2016, the World Health Assembly adopted a Global Health Sector Strategy on Viral Hepatitis with the goal of eliminating the disease by 2030 [30].

Worldwide prevalence	>2 billion	(103-105)
In developed countries	2.2 million	(106,107)
In Pakistan	>40 million	(50,108-110)

Table I: Epidemiology of HBV infection

Situation of HBV Infection in Pakistan: Pakistan is among the worst nations on the planet when it comes to HBV infection. Various surveys were conducted to determine the pervasiveness of HBV in various parts of Pakistan. HBV is very prevalent in Pakistan, with 7–9 million people infected and a ubiquity rate of almost 3–5%. HBV endemicity in Pakistan is intermediate, with an estimated 3-5 percent ratio. Interior Sindh, Karachi, and Southern Punjab, Kurrum agency, Northern Waziristan, and some regions of Lahore are said to have an HBV preponderance of more than 5%. According to reports, HBV is associated with chronic liver disorders 44.45% of the time in Pakistan [31].

Transmission: Virus is communicated through percutaneous and per mucosal subjection to the body fluids of invaded person. The virus can be spreaded by human transmission channel such as interaction with an exhorted person's blood or other bodily fluids. Such fluids constitute saliva, vagina, menstrual and seminal fluid. It can be transmitted through the interchange of bodily fluids and is stable on inert items for at least seven days. HBV is 50–100 times extra contagious than HIV [32]. Virus conveyance principally in two different configurations which are explained below:

Vertical transmission: In that form of configuration infectious particle is dispatched at the time of child birth (from mother to the baby)[33].

Horizontal transmission: Pathogens are dispersed between the representative of the same species, that are not in a hierarchical relationship. In this form of transference virus is spread by contact of healthy individual with infected personnel's body fluids comprising blood, sputum, menstrual, semen and vaginal fluids [34]. In developing states means of communication are: perinatal (from mother to baby in the course of delivery), Premature infancy infections (by close contact with contaminated items), Hazardous needle practice, contaminated blood diffusions, Vulnerable sexual intercourse. Common personal items (blades, scissors, nail clippers) with a sick person. In Pakistan the incidence of hepatitis is more familiar in rural community as compared to urban community. On the other hand, it is also high in multipara relative to primigravida. It is because of that, expecting mothers are at high risk of emerging anemia resulting need of blood transfusion which might not be secure [35]. HBV infection is most familiar in hairdressing salon visitant it is as a result of unintelligence with reference to the spread of HBV communication. In Pakistan, barber shops are not decontaminated. Even in developing countries upskilled medical workers apply inappropriate antisepticise materials for example tools used in dental practice and other laboratory items. HBV may also originate by endoscopy as instruments of endoscope came in touch with body fluids [36]. It is elucidated that HBV communication through vertical transmission is a reason of HBV interconnected demise around 21% planetary. Whereas geographically it varies from Eastern Mediterranean to western Pacific about 13-26% consecutively. It also reported that in a latest analysis in Africa, there is elevated seropositivity in expecting

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mothers, regardless of span, consistency, fertilization age, locality, blood transfusion record, dental procedures and piercings. In Africa, the frequency of HBV infectivity is considerably large, with the second biggest number of chronically HBV-infected people.

Immunopathogenesis of HBV: The constancy of the HBV is facilitated by its silent character [37], which efficiently develops invasion in a non-cytopathic way. It does not elicit a host immune reaction in hepatic cells. It seems to be frequently subjected to intracellular antiviral components. HBV commences an intricate proliferative cycle that sustains viral viability in human hepatocytes during infection. HBV penetrates human hepatocytes through a series of stages. The virus first adheres to the host cell surface by adhering to its aspects such as heparan sulphate proteoglycans, after which it engages with its receptors more precisely and with increase binding specificity. Viral-receptor interfaces are considered to produce virus incorporation into cells that is mediated endocytosis. The HBV life process typically involves a period in which HBV DNA is transcribed to a very stable double-stranded circular DNA structure described as covalently closed circular DNA (cccDNA) within the hepatocyte nucleus. This cccDNA is very conservative and termed as minichromosome. The DNA of the HBV is also united into the DNA of the host. Covalently closed circular DNA functions as a template for viral RNA transcription, may remain indeterminately within the long-lived hepatocyte nucleus, and acts as a pool for virus proliferation. Different host factors including transcriptional factors stimulate the cccDNA transcriptional activity. The viral cccDNA comprise viral transcript production with the help of RNA Polymerase II. This transcript is transferred to cytoplasm where viral proteins are translated. The fate of HBV infection is resolute by the host-virus association, which is coordinated by the protective immune system [38]. It should also be remembered that the virus-specific T cell activation is a critical aspect in the development of HBV contamination. The progression and outcome of the disease may have an impact on viral variations. The character of host variables in illness advancement is not entirely identified.

Histopathological Aspects: Acute hepatitis B: The key elements of histological findings in an acute infection are as follows: Lobular disorganization, Ballooning deterioration, Numerous apoptotic bodies, Kupffer cell stimulation, Lobular and portal lymphocytic inflammation [39].

Chronic hepatitis B: The key elements of histological findings in chronic infection usually include: Portal lymphocytic inflammation, Spotted lobular inflammation [40].

Clinical manifestations: HBV infection can result in a wide range of clinical signs, including silent early detection, acute self-limiting disease, symptomless liver failure, prolonged hepatitis with fibrosis, and hepatocellular carcinoma (HCC). Acute viral hepatitis is the etiological agent for HBV infection. Symptoms may take up to six months to emerge after exposure. Early signs and symptoms of HBV infection are lethargy, nausea, poor appetite, vomiting, pyrexia, headache, muscle pain, joint pain, gastrointestinal disturbances, dark urine and jaundice. It is observed that the illness in acute hepatitis B can persist anywhere from one to six weeks, however it can also be extended and fulminant. The age of the individual who comes into touch with the virus has a big impact on how quickly the illness progresses from acute to chronic. If a person's immune system would be unable to void the virus six months beyond acute HBV infection, they are referred to be chronically afflicted. Generally chronic HBV infection is symptomless but it may lead to hepatic failure. The probability of developing end-stage liver pathologies increases as chronic HBV infection advances, leading to an increase in mortality. Even though it can induce chronic hepatitis, fibrosis, cirrhosis, and HCC in rare cases, this infection is usually asymptomatic and causes no significant liver damage [41].

Diagnosis: HBV infection has three major markers including, the antigen on the surface of the cell (HBsAg), which signals the presence of illness, Total core antibody (HBcAb) which shows current or previous infection and Surface antigen antibody (HBsAb), which suggests immunity.To confirm the existence of HBsAg in HBsAg-positive samples, secondary markers are used:Hepatitis e antigen (HBeAg), a marker for significant viral replication and contamination.The hepatitis e antibody (HBeAb), which signals poor viral replication and contamination.The IgM core antibody (HBcIM), which suggests the presence of a current or recent illness.Appropriate testing should be guided by a person's history, age, risk factors, immunization records, and previous test results. Blood tests are used to determine if you have HBV infection.

Treatment: Acute infection infection does not typically require medication, and even most people recover on their own. In less than 1% of patients, early antiviral therapy may be recommended if the virus progresses quickly (fulminant hepatitis) or if they are immunocompromised. In order to reduce the risk of liver cancer, treatment of persistent infection may be required. Individuals who have been contaminated for a extensive period and go through persistently high serum alanine aminotransferase, a biomarker of liver damage, as well as high HBV DNA levels, are candidates for treatment. Depending on the drug and

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genotype, treatment might take from six months to a year, The duration of treatment when medicine is taken by mouth, on the other hand, is more varied and generally exceeds one year. The treatment minimizes the viral load by suppressing viral proliferation in the liver [41].

CONCLUSIONS

To summarize, the findings of this work shed light on a number of significant features of HBV molecular epidemiology that are critical for identifying populations at risk of contracting HBV and developing severe disease, as well as posing a danger of transmission through various modalities. Persons infected with HBV have a higher risk for progression of disease and complications and must have rigorous surveillance and treatment.

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