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Introduction to Chronic Hepatitis B Infection

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Abstract: *Millions of humans worldwide are impacted by chronic hepatitis B infection, which is brought on by the hepatitis B virus (HBV). A chronic viral infection is the underlying cause of this illness, which can result in serious liver consequences such as cirrhosis, liver failure, and hepatocellular cancer. The course and management of chronic hepatitis B are influenced by its dynamic nature, which includes many stages that span from immune-tolerant to immune-active. In order to lower the disease burden and related problems, this review aims to provide a thorough knowledge of chronic hepatitis B. It emphasises the need of early diagnosis, appropriate monitoring, and access to efficient antiviral therapies. Moreover, it highlights the continued research endeavours aimed at creating more effective treatments and vaccinations, with the ultimate goal of eliminating this enduring viral illness..*

Keywords: hepatitis B

I. INTRODUCTION

Given that the hepatitis B virus (HBV) is carried by approximately 300 million people globally, hepatitis B is a disease of great global relevance[1]. Up to 80% of primary liver cancer cases are caused by HBV, making it the leading cause of cancer-related death worldwide. Significantly contributing to cancer-related deaths, HBV is the second biggest cause of death after tobacco use[1,2]. In areas where the percentage of carriers of HBV is more than 10%, the virus may be responsible for up to 3% of all deaths. The reason for this high death rate is because around 30% of people who are long-term HBV carriers and live for at least 30 years are predicted to die from long-term effects of their infection, such as primary liver cancer or cirrhosis[3].Out of the 5 billion people on the planet, about 3.5 billion live in regions with moderate to high HBV prevalence (defined as a chronic carrier rate more than 2%). In addition, 122 million or more newborns are born every year, and a significant portion of them run the danger of contracting the virus permanently[4].The enormous cost that chronic Hepatitis B poses to the general public's health as well as the possibility of serious long-term consequences like cirrhosis and liver cancer is highlighted by these statistics figures. In order to stop the spread of this viral illness and lessen its long-term effects, it also highlights the urgent need for extensive immunisation campaigns and successful public health campaigns[5].

A significant geopolitical aspect of the global distribution of HBV carriers is that more than 90% of these people live in underdeveloped nations, where it is exceptionally difficult to acquire quality healthcare and the financial means to support them[6]. Of the 122 million babies born in 1985, an estimated 1.3 million were predicted to die from liver-related conditions caused by HBV[7]. Notably, the largest percentage of these deaths—roughly 76%—was predicted to happen in Asia, while the next-highest percentage—roughly 18%—was predicted to occur in Africa.This data indicates a disproportionate burden of the illness in countries where healthcare resources are already stretched, emphasising a stark imbalance in the distribution and effect of Hepatitis B, especially in developing regions[8]. A comparative investigation reveals that Hepatitis B is a disease that distinguishes itself significantly from other prevalent infectious illnesses, such as AIDS. This placement is a result of the pressing need to give control and preventative initiatives top priority in order to lessen the severe impact it has on impacted people[9]. The high frequency, high potential death rates, and scarcity of resources in these areas highlight the urgent need for significant international efforts and funding to stop the spread of this illness[10,9].

Individuals diagnosed with chronic Hepatitis B Virus (HBV) infection should be provided with comprehensive counseling on both pharmaceutical and non-pharmacological strategies to manage their condition. Non-pharmacological management plays a vital role in maintaining overall health and preventing further liver damage[11].

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Key elements of non-pharmacological management strategies for chronic HBV may include:

- **Diet:** Patients should be advised to maintain a healthy, balanced diet. This often includes reducing the intake of processed foods, saturated fats, and refined sugars while increasing the consumption of fruits, vegetables, and whole grains. A balanced diet helps support the immune system and overall liver health[12].
- **Rest and Stress Management:** Adequate rest and stress reduction are essential for supporting the immune system and overall well-being. Stress can impact the immune response, so stress reduction techniques can be beneficial[12].
- **Maintaining Fluid Balance:** Staying hydrated is important for liver health. Patients should be encouraged to consume an adequate amount of water daily, unless otherwise advised by their healthcare provider due to specific health conditions[12].
- **Avoidance of Alcohol and Hepatotoxins:** It is critical for individuals with chronic HBV to completely avoid alcohol and other hepatotoxins. Alcohol can exacerbate liver damage in individuals with chronic liver disease[13].
- **Disclosure to Sexual Partners:** Patients are advised to inform their sexual partners about their HBV status. Partners should be encouraged to undergo HBV testing and vaccination if not previously immune. Safe sexual practices, such as using condoms, are also recommended to prevent transmission[12].
- **Avoidance of Needle Sharing:** Individuals with HBV should avoid sharing needles, as this is a significant mode of transmission[12].

Epidemiological factors :

The age at which people are infected is the most important epidemiological factor for Hepatitis B, since it has a significant impact on the disease's prevalence and directly affects the development and use of preventative measures[13]. The principal mechanism of transmission and infection age are strongly related.Hepatitis B infections mostly strike adults in areas where the virus is not prevalent, and they frequently spread through sexual contact. In contrast, infections mostly affect children and newborns in regions with intermediate to high endemicity. In these areas, mother-to-child transmission after childbirth or intimate child contact are the most typical ways that the disease is spread.In regions where HBV endemicity is low, infections often manifest in maturity and are frequently associated with sexual contact-borne transmission[14]. On the other hand, newborns and young children are the main source of transmission in areas with intermediate to high endemicity. During childbirth, mother-to-child transmission or intimate personal contact between children are the most common routes of transmission. It's crucial to remember that if an individual contracts HBV during infancy or early childhood, their chance of developing chronic HBV infection increases significantly[15].A key consideration in developing and implementing preventative measures is the difference in the age of infection and the main modes of transmission across areas with low and high endemicity. Preventive strategies may emphasise encouraging safe sex practises, granting access to healthcare, and putting in place targeted vaccination programmes for high-risk individuals in areas where HBV infections are primarily acquired in adulthood[16]. However, preventive efforts should focus on interventions like widespread infant and child vaccination, preventing mother-to-child transmission, and encouraging hygiene and disease control within communities where children interact closely in areas where childhood transmission is common. For the purpose of developing and putting into practise efficient preventative measures based on the unique epidemiological profile of a given location, it is imperative to acknowledge the age of infection as a crucial element that determines transmission pathways. This knowledge facilitates the intelligent distribution of resources, including immunisationprogrammes and public health campaigns, to reduce the incidence and spread of Hepatitis B17,18.

NATURAL HISTORY OF CHRONIC HEPATITIS B INFECTION :

The natural history of chronic Hepatitis B infection has been classified into three distinct stages by a National Institutes of Health (NIH) workshop. These stages illustrate the progression and characteristics of the infection over time[19,20].

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Stage 1: Immune Tolerance Phase:

Duration: This initial phase typically lasts for 2–4 weeks in healthy adults. However, it can extend for several decades in individuals infected during neonatal or early childhood[20].

Characteristics: The immune tolerance phase is marked by active viral replication without symptoms. It is evidenced by the secretion of Hepatitis B e antigen (HBeAg) and high levels of serum HBV DNA. Importantly, there is no significant increase in serum alanine aminotransferase (ALT) levels during this phase. ALT is an enzyme found in the liver, and elevated levels often indicate liver damage[20].

Immune Response Development: Subsequently, an immunologic response might start to develop. HBeAg is still secreted during this transition, but serum HBV DNA levels decline as the number of infected cells decreases. This phase signifies a reduction in viral replication[21].

The absence of high ALT levels is due to the immunological tolerance phase, which is a crucial time where vigorous viral replication occurs without severe liver damage, especially when it lasts longer. Even said, the absence of symptoms indicates that the virus is actively replicating during this period, which may eventually impede the advancement of liver disease[22].

Patients maintain HBsAg positivity during HBeAg seroconversion, signifying the continued presence of surface antigen, and the viral DNA is incorporated into the hepatocyte genome of the host. Furthermore, HBV DNA is found in serum by sensitive polymerase chain reaction (PCR)-based tests, indicating that the virus is still replicating in the liver[23]. This stage, which is also referred to as the "inactive carrier state," allows individuals to continue living their whole lives with just little liver damage. Nonetheless, reactivation of HBV replication may occur spontaneously or as a result of immunosuppression in some individuals. This reactivation may increase the chance of developing cirrhosis and the liver cancer hepatocellular carcinoma (HCC). Reactivation of HBV replication following an interval of inactive carrier status is associated with a heightened risk of sequelae, including cirrhosis and HCC[24,25]. It is essential to keep an eye out for any indications of liver damage and viral reactivation in these individuals in order to start treatment as soon as possible and stop the condition from getting worse. Unless these people are immunosuppressed, it is unlikely that the Hepatitis B virus would re-infect or reactivate in these situations. Still, it is rare for people with established chronic Hepatitis B infection to spontaneously lose HBsAg[26].

A considerable percentage of individuals may have illness progression following the seroconversion from HBeAg positive to negative. This kind of persistent Hepatitis B, also known as HBeAg-negative chronic Hepatitis B (HBeAg-negative CHB), is more frequently seen in areas where infection happens during infancy or at birth. Patients with HBV variations carrying mutations in either the precore region or the core promoter of the HBV genome are known as HBeAg-negative CHB patients. Although they have an effect on HBeAg synthesis, these alterations have no effect on viral replication. Thus, while maintaining continuing HBV replication, people in this condition display low or undetectable levels of HBeAg[27,28].

This illness is particularly essential to identify since it represents a unique stage of chronic Hepatitis B and is frequently linked to an increased risk of the advancement of liver damage. Since these patients may still be at risk for problems even in the absence of HBeAg, it is crucial to monitor their liver function and the course of their condition. Treatment approaches vary often for this subset of patients, necessitating a customised strategy based on the unique features of HBeAg-negative CHB[29,30].

FACTORS INFLUENCING THE NATURAL HISTORY OF CHRONIC HEPATITIS B

The age of the patient during infection, in addition to a number of other host, viral, and environmental variables, determines the rate of progression to cirrhosis and/or HCC.

Age at Infection : A viral infection that affects the liver, hepatitis B can result in both acute and chronic illnesses. The course of an infection might be influenced by the age at which a person is exposed to the virus. Compared to people infected as adults, individuals who get hepatitis B perinatally—during childbirth—or as infants are more likely to experience chronic infections.One of the most important factors in deciding whether an infection becomes chronic is the immune system's reaction to the virus. Early infancy is a time when the immune system is still developing, which may make it more likely for the virus to cause a chronic illness. Cirrhosis and liver cancer are two major liver problems that can result from persistent hepatitis B infections[31].

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The data from a large cohort study of Alaskan natives with chronic HBV infection suggests that the loss of HBeAg is more likely to occur in older carriers compared to younger individuals. The study found that the probability of spontaneous HBeAg loss within 5 years of diagnosis varied with age. Specifically:
For carriers aged 0–18 years, the observed probability of HBeAg loss within 5 years was 0.39.
For carriers aged 19–30 years, the observed probability of HBeAg loss within 5 years was 0.56.
For carriers aged 31–78 years, the observed probability of HBeAg loss within 5 years was 0.45.
High viral replication without a commensurate immune-mediated assault on infected liver cells characterises this immune-tolerant phase. During this stage, the immune system is, in a way, tolerant to or resistant to the virus. Consequently, there may be no discernible damage or inflammation to the liver histology, and liver enzyme values may stay within normal ranges. It's crucial to remember that the immune system may eventually shift from an immunological-tolerant to an immune-active phase, which might affect liver function and histology. Numerous host and viral variables can have an impact on the complicated dynamics driving this transformation[32,33].
Host Factors: Cirrhosis Ratio: The statement mentions that the ratio of males to females with cirrhosis resulting from chronic HBV infection is approximately 2:1. This suggests that males are more likely to progress to cirrhosis as a complication of chronic HBV infection compared to females. Cirrhosis is a late-stage scarring of the liver that can result from long-term liver damage[34].
Hepatocellular Carcinoma (HCC) Incidence: The statement also notes that the incidence of hepatocellular carcinoma (HCC), a type of liver cancer, is three to six times higher in men than in women with chronic HBV infection. This gender disparity in HCC rates is a significant observation and underscores the importance of considering gender-specific factors in understanding the natural history of chronic HBV infection[35].
These gender disparities in the course of the disease are probably due to a variety of complex variables, including behavioural and biological ones. For example, the immunological response to the virus may be influenced by the hormonal variations between males and females. Furthermore, the gender differences in illness outcomes that have been noted may be attributed to lifestyle and behavioural variables, such as alcohol usage[36].

Viral Factors :
Active Replication and Disease Progression : Patients with active replication of the hepatitis B virus (HBV), as indicated by detectable HBV DNA in serum, are suggested to be at a greater risk of disease progression compared to those without detectable HBV DNA. Active viral replication can contribute to ongoing liver damage and inflammation[37].
Immune Tolerant Phase : According to the statement, even in cases when there is no discernible liver damage, individuals in the immune-tolerant phase of the illness may have a high level of viral replication. A minimal immune response to the virus characterises the immunological-tolerant phase, which permits high viral replication levels without causing noticeable liver damage[36,37].
Cirrhosis and Prolonged Viremia : It is hypothesised that cirrhosis, a late-stage complication of chronic liver disease, arises from sustained immune death of hepatocytes that present antigens. Extended viral persistence in the circulation, or prolonged viremia, may impact the course of the illness and perhaps play a role in the development of cirrhosis[37,38].
Risk of Hepatocellular Carcinoma (HCC) : The host immune system and the direct effects of viral replication and genomic integration are linked to the risk of hepatocellular carcinoma (HCC), a form of liver cancer. Necroinflammation, or inflammation linked to cell death, and hepatic regeneration, or the liver's capacity to replace and repair injured cells, are examples of these variables[39].
Exogenous Factors : Hepatitis A Virus (HAV) Coinfection: Acute hepatitis A infection can cause a more severe liver disease in individuals with chronic hepatitis B. Additionally, superimposed acute hepatitis A on chronic hepatitis B may increase the risk of fulminant hepatitis (severe, life-threatening liver failure). Vaccination against hepatitis A is recommended for individuals with chronic hepatitis B to prevent this complication[40].
Hepatitis C Virus (HCV) Coinfection: Coinfection with hepatitis C can lead to accelerated liver disease progression. It increases the risk of cirrhosis and hepatocellular carcinoma (HCC)compared to individuals with hepatitis B or C infection alone. Management strategies for individuals with dual hepatitis B and C infection are complex and may involve antiviral therapy targeting both viruses[40,41].

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Hepatitis B vaccines :

Hepatitis A Virus (HAV) Coinfection: People with chronic hepatitis B may develop a more severe liver disease as a result of an acute hepatitis A infection. Furthermore, the chance of developing fulminant hepatitis—severe, life-threatening liver failure—may rise when acute hepatitis A is layered over chronic hepatitis B. For those with chronic hepatitis B, vaccination against hepatitis A is advised in order to avoid this consequence[42].

Hepatitis C Virus (HCV) Coinfection: A co-infection with hepatitis C may cause the liver disease to proceed more quickly. Compared to those who just have hepatitis B or C infection, it raises the risk of cirrhosis and hepatocellular carcinoma (HCC). Antiviral medication directed against both viruses may be part of the complicated management methods for persons with dual hepatitis B and C infections[43,44].

Hepatitis D Virus (HDV) Coinfection: Only those who have already had hepatitis B are susceptible to hepatitis D infection. A increased chance of cirrhosis and hepatocellular cancer are among the consequences of more severe liver disease that can arise from HDV superinfection or coinfection with chronic hepatitis B. Hepatitis D treatment options are limited, however antiviral medication is being used to manage hepatitis B[45,46].

Pioneering Development:

The hepatitis B vaccines licensed in 1981 were groundbreaking as they were the first vaccines of their kind manufactured from human plasma.

Notably, these vaccines held the distinction of being the first anti-cancer vaccines available for human use. This highlights their potential in preventing liver cancer associated with chronic hepatitis B infection[47].

Global Distribution:

Although vaccine supplies were initially limited and primarily available in private sector markets, by the end of 1988, there were 13 manufacturers of these vaccines worldwide.

Over 50 million doses of the vaccine had been distributed globally by the end of 1988, indicating a significant expansion in production and distribution[47].

Safety and Effectiveness:

Results from initial studies, which continue to be confirmed, indicated that these vaccines are among the safest and most effective vaccines ever produced.

The vaccines were found to have an extremely low frequency of initial side effects, making them well-tolerated by recipients[47].

Blood-Borne Pathogen Safety:

Under current manufacturing conditions, these vaccines were designed to ensure the absence of transmission of agents found in human blood, including the human immunodeficiency virus (HIV).

This emphasizes the high safety standards implemented in the manufacturing processes[47,48].

Strategies for control :

Integration with EPI:

The primary recommendation is for the integration of HBV mass immunization into the Expanded Programme on Immunization (EPI), a multinational effort aimed at immunizing children worldwide against preventable childhood diseases[49].

Multinational Effort:

The EPI is described as a multinational effort designed to immunize all children globally against diseases that are preventable through vaccination[49,50].

Current List of Diseases in EPI:

The EPI's current list includes six immunizable diseases: diphtheria, measles, pertussis, polio, tetanus, and tuberculosis. These diseases are officially part of the EPI's immunization activities[50].

Expansion to Include Hepatitis B:

Under more limited conditions, the EPI has expanded its scope to include hepatitis B. This extension is conditional on countries having the economic capacity to purchase the vaccine and a chronic HBV carrier rate exceeding 2.5%[50,51].

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Economic Capacity Criteria:

The inclusion of hepatitis B in the EPI is contingent on the economic capacity of countries. Those with the financial means to acquire the vaccine are considered for inclusion in the program[52].

Targeted Approach to High Carrier Rates:

The criteria for including hepatitis B in the EPI focus on countries where the chronic HBV carrier rate exceeds 2.5%. This reflects a targeted approach to addressing regions with a higher burden of hepatitis B[52].

II. CONCLUSION

In conclusion, millions of people worldwide are impacted by chronic hepatitis B infection, which poses serious hazards to liver health. As the causing agent, the hepatitis B virus causes a chronic viral infection that can worsen into serious liver diseases. The dynamic nature of immune-tolerant to immune-active stages in chronic hepatitis B highlights the intricacy of the illness's progression and treatment.

The analysis underscores the paramount significance of prompt diagnosis, attentive monitoring, and availability of efficacious antiviral medications in reducing the severity of the disease and averting its related consequences. Ongoing research initiatives are essential to improving our understanding of the intricacies of chronic hepatitis B and developing more effective treatment strategies. The development of more potent medications and vaccines is essential if this persistent viral disease is to be completely eradicated.

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