Natural History of Hepatitis B Virus (HBV) Infection

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Abstract

Chronic hepatitis B is a global health burden and increasingly a public health concerns in US due to changing immigration pattern from mostly Western European immigrants to Asian, African and Eastern European where prevalence of chronic hepatitis B is higher. Therefore in these particular at risk populations, education of health providers and patients is vital in achieving successful disease prevention and control. Understanding the natural history of this complicated and dynamic disease will lay the ground works for comprehensive management of chronic hepatitis B. In this article, the natural history particularly the four phases of chronic hepatitis B and the outcome of the disease such as cirrhosis and HCC and the risk factors for disease progression and HCC development will be discussed. The importance of screening and vaccination is emphasized particularly the success of HCC prevention in countries with population-wide vaccination program. It is with the hope that this review will enhance and educate the primary health provider for the most at risk population of chronic hepatitis B in US and therefore alleviate the burden of this disease.

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Key Words: *Hepatitis B Virus (HBV), Infection*

Introduction

It has been estimated that more than 2 billion people in the world have been exposed to hepatitis B and up to 400,000 are chronically infected with hepatitis B virus.[1] It is the major cause of hepatocellular carcinoma globally. In US, due to paradigm shift of immigration pattern from mostly Western European to mostly Asian, African and Eastern European in the last three decades. The prevalence of chronic hepatitis B has increased significantly in US. It is now estimated the prevalence rate of chronic hepatitis B in US is upward to 2 million.[2] This is especially true in Chinese community with an estimation of 10% rate. It is then incumbent upon the health care providers for this population to equip themselves with a solid knowledge of hepatitis B. The natural history of chronic hepatitis B has been studied extensively since the early 1980's even before the molecular technology of PCR (Polymerase Chain Reaction) became widely used in the study of hepatitis B. It is now clearly understood that the natural history of chronic hepatitis B represents a dynamic interaction between the host immune system and the virus. This makes the natural progression of chronic hepatitis B a very fluid situation. In this review, I will discuss the dynamic natural history of chronic HBV infection and identify factors that have been associated with disease progression and the development of hepatocellular carcinoma (HCC) and further to discuss disease prevention and control for this dreadful but preventable disease burden on Chinese community in US.

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Risk of Chronic HBV After Acute Infection

It has been well established in many studies that perinatal and early childhood infection carry a much higher risk of developing chronic hepatitis when compared to adult exposure, a differences of 90% vs 5%.[3] However this risk can be reduced with perinatal active (Hepatitis B vaccine) and passive (Hepatitis B Immune Globulin, HBIG) immunization to less than 5% chronicity as eloquently shown in the Taiwanese study with its universal implementation of this vaccine policy in Taiwan-the first in the world. This strategy has actually reduced HCC rate in children who were vaccinated prompting WHO to declare that HBV vaccine as the first cancer prevention vaccine.[4,5,6]

Factors Associated with Risks of Hepatocellular Carcinoma

It have been clearly shown that chronic hepatitis B infection with positive HBsAg carry an increased risk of HCC in population-based cohort studies in Taiwan and Alaska.[7,8] In addition, other factors in recent years have been found to be associated with increasing risk of HCC development in patients with positive HBsAg. These can be divided into:

1) **Host Factors:**
   Age: Those patients with chronic hepatitis B older than 40 has an increased risk of HCC when compared with younger age bracket.[9]
   Gender: Men by far has been associated with higher risk of HCC compared to women in many cohort studies with an adjusted relative risk of 2.1 to 3.6 in men more than women.[9]
   Family History of HCC: Family history of HCC has been linked to increased risk of HCC in chronic hepatitis

B patients. In a study from Taiwan looking at the first degree relatives of 553 CHB patients with HCC compared with 4686 CHB patients without HCC as control, the first degree relatives of the HCC group has a higher rate of HCC. This observation was also confirmed by an US study. An Italian cohort study also found an increased odds ratio of 70.1 among those who have CHB and a family history of HCC.[10,11,12]

2) **Environment Factors:**
Aflatoxin found in contaminated food or soils consumed by human has been found to cause an increased risk of HCC as reported from sub-Sahara Africa and Southeast Asia and China. In villages near Shanghai, a study found the first convincing evidence of linkage of Aflatoxin and HCC in CHB patients. It has been postulated that P53 gene mutation caused by Aflatoxin were the culprit.[13,14,15]

3) **Life Styles Factors:**
Alcohol consumption: Alcohol consumption has been found in multiple studies in US, Japan and Korea. For instance, in a longitudinal study of HBV patients with or without habitual alcohol consumption (>27gm/d), a 5-fold increase in the relative risk was noted in Japan. In Korea a 50g/d alcohol consumption were associated with an increased risk of HCC.[16,17]
Obesity and diabetes mellitus: Both a component of metabolic syndrome, have been implicated in multiple epidemiological data review and studies to be associated with increased risk of HCC independent of other confounding factors including alcohol and viral hepatitis.[18,19,20]

4) **Co-morbid Factor:**
Co-infection with HCV has also been with an increased risk of developing HCC.[21,22]

5) **Viral Factors:**
HBsAg: In 1981, Beasley and his colleagues in Taiwan reported their landmark study connecting HBsAg positivity with risk of HCC. The relative risk of HCC was about 100 in HBsAg positive patients.[23] Furthermore, Asian hepatitis B carriers (ie HBsAg positive) without cirrhosis remain at risk for HCC regardless of their HBV replicative status contrary to most other causes of chronic liver disease where cirrhosis is a pre-requisites for HCC. This is the reason behind the AASLD's recommendation to start HCC surveillance in Asian male and female chronic hepatitis B carriers regardless if they have cirrhosis or active disease.[24]

HBeAg: Yang et al in 2002 reported a large prospective study of chronic hepatitis B in Taiwan for a ten years follow up and found that positive HBeAg patients had a much higher risk of developing HCC and remains a risk factor after adjusted for other covariates.[17]

HBV variants-pre-core and basal core promoter mutants, viral genotype: In a long term cohort study of Asian hepatitis B patients in LA, Tong et al found HBV viral variants with basal core promoter mutation (A1762T/G1764A) and precore mutation (G1896A) are associated with increased risk of developing HCC over a mean follow up of 112 months. And presence of genotype C is also associated with higher risk for HCC as also reported in another study from Taiwan.[25,26] Longer studies with more patients would be needed to confirm these findings.

HBV DNA level: In a recent long term observational study of outcomes of a large cohort of chronic hepatitis B patients, it was noted that Taiwanese male age older than 40 (REVEAL –B), higher viral level (HBV DNA level greater than 20,000 IU/ml) over time is associated with increased risk of developing HCC and cirrhosis. This remains an independent risk factor even after adjusted for other known covariates such as HBeAg status, serum aminotransferase level, gender, age and alcohol consumption.[27,28] It has been reported by Liaw et al that viral suppression with anti-viral agent can prevent disease progression and reduce the incidence of HCC in patients with advanced fibrosis or cirrhosis.[29] However the question remains if reducing HBV DNA level in patients with no advanced disease can also prevent progression of disease and reduce the risk of HCC.

Table 1. Natural History of Chronic Hepatitis B Infection.

HBV Phase*	HBeAg	HBV DNA Level	Liver histology
Immune Tolerant	Positive	high	Normal to Minimal
Immune Active	Positive or Negative	High but lower than immune tolerant	Mild to Cirrhosis
Inactive	Negative	Low or undetectable	Mild to Cirrhosis
Resolved	Negative	undetectable	Normal to Mild**

*Risk of HCC remains in all phases
**Depends on clinical course of the liver disease, moderate to severe fibrosis may be present.

Natural History and Progression of HBV

The natural history of chronic HBV infection is a complex and dynamic process. The course of the disease can differ quite significantly from one infected patient to another.[30] It has been estimated by different natural history studies around the world that the lifetime risk of serious complications is approximately 25% for HCC and 10-15% for decompensated cirrhosis. In order to understand in a more simplistic way, there are four clinical phases of chronic HBV infection identified as follows (**Table 1**): The immune tolerance phase occurs primarily in patients who have been infected at birth from hepatitis B "e" antigen (HBeAg) positive mothers and is characterized by presence of HBeAg, normal ALT, very high HBV DNA levels usually > 200,000 IU/mL and no or minimal histological inflammation or fibrosis. This is usually followed by so-called immune reactive phase due to host immune recognition of HBV in the hepatocyte which is clinically characterized with ALT levels rise and HBV DNA levels begin to decline and liver inflammation and fibrosis occur.[31] Clinically it has also been called "HBeAg positive chronic hepatitis B". Eventually close to 90% of persons will experience HBeAg seroconversion and develop antibody to HBeAg (anti-HBe) though the time to seroconversion differ from each individuals and hence different degree of liver injury and fibrosis even cirrhosis. Most of these individuals will evolve into the inactive hepatitis B phase characterized by normal ALT and low levels (usually below 2,000 IU/mL) or undetectable HBV DNA by PCR method.[32] However, as many as 20% will revert back to the HBeAg positive immune active phase (reverse-seroconversion) and another 10-20% will remain in the anti-HBe immune active phase (HBeAg negative chronic hepatitis B).[33] Flares of ALT elevations that are usually asymptomatic often occur with reverse-seroconversion and seroconversion. These episodic flares will cause significant liver damage and often progress to advanced fibrosis or cirrhosis. In addition, 10-20% of persons who are in the inactive phase can reactivate to the anti-HBe immune active phase. For those patients who remain in the inactive phase, approximately 0.5%/year will lose HBsAg and eventually develop HBsAb. At this stage the risk of HCC and cirrhosis decrease significantly, but HCC can still occur years later particularly in those who has advanced fibrosis or cirrhosis at the time when they seroconverted.[32] Thus, the natural history of chronic HBV infection is unpredictable and dynamic because patients can develop liver inflammation and fibrosis slowly or rapidly which depends on the interaction of host immune system and virus. A person can remain inactive and has a benign outcome or may reactivate and leads to cirrhosis and HCC.

Outcomes of chronic HBV infection include progression to cirrhosis, liver failure, and HCC. The annual incidence of cirrhosis has been estimated to be 2-4% for HBeAg-positive and 3-10% for HBeAg-negative patients.[34] The annual incidence of HCC has been estimated to be <1% for non-cirrhotic carriers and 2-4% for patients with cirrhosis.[27]

Hepatitis Delta virus (HDV) is an RNA virus which infect only those patients who carry HBsAg. HDV need HBsAg as an attachment to establish human hepatocyte infection. It has been found mostly in the Mediterranean region and in US the risk factors are intravenous infection and sexual transmission.[35] The HDV has an unique RNA genome, encoding its only known protein-delta antigen-which are encapsulated in a lipid envelope containing HBsAg stolen from a requisite HBV co-infection. There are two mode of HDV infection. First, simultaneous infection of HBV and HDV can cause severe hepatitis with mortality but if recovered the majority will develop immunity against both HBV and HDV.[36]. Another mode is HDV super-infection on someone who already harbors chronic hepatitis B. When HDV superinfection occurs in chronic hepatitis B patients, fulminant hepatitis remains an increased risk and they almost always resulted in chronic infection of both HBV and HDV. And their liver disease tends to progress more aggressively. HDV probably cause the most severe form of viral hepatitis.

Conclusion

In a recent report from Institute of Medicine about the current state of viral hepatitis awareness or lack of it, they concluded, "there is a lack of knowledge and awareness about chronic hepatitis on the part of health care and social service providers, as well as among at-risk populations, members of public, and policy makers. Due to the insufficiency understanding about the extent and seriousness of this public-health problem, inadequate public resources are being allocated to prevention, control, and surveillance programs". As part of their recommendation to remedy this discrepancy, it was advocated to improve provider and community education on viral hepatitis. 37 Therefore, this review of the natural history of chronic hepatitis B is written in the hope that enhancing the knowledge of the clinicians who have the highest chance of encountering chronic hepatitis B patients (Chinese Immigrants) in their practice can improve the care of their patients. As it has been clearly demonstrated that hepatitis B vaccination can reduce the incidence of HCC in children and prevent HBV infection thus preventing HBV related cirrhosis. It cannot be over emphasized that vaccinating unprotected population is an extreme cost-effective measure in combating this endemic disease.

In addition, treatment of persons with advanced compensated fibrosis and cirrhosis can decrease the incidence of hepatic decompensation, liver related death and HCC.[52] Particularly with the advent of new relatively safe and potent antiviral agents directed against HBV, the potential to change the natural history of HBV is promising. In fact, Practice Guidelines developed by the three major liver societies, the American Association for the Study of Liver Diseases (AASLD), the Asian Pacific Association for the Study of the Liver (APASL) and the European Association for the Study of the Liver (EASL) all recommend treatment for those found to have moderate hepatic inflammation or fibrosis, assuming that many of these patients might progress to cirrhosis. It therefore is incumbent upon us, the clinicians, to

act upon this very important but underappreciated disease burden.

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