Natural History of Hepatitis B and Prognostic Factors of Disease Progression

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INTRODUCTION

Hepatitis B virus (HBV) infection is a serious global health problem responsible for between 500,000 and 1.2 million deaths annually from cirrhosis and hepatocellular carcinoma (HCC) [1]. Although the HBV vaccination has significantly reduced the number of new infections, a large reservoir of HBV infected individuals remains and it has been estimated that worldwide 360 million people are chronic carriers of the virus [1]. The clinical course and outcome of HBV infection is greatly influenced by age at infection, the level of HBV replication and host immune status. Thus hepatitis B is a heterogeneous disease that may either resolve spontaneously or progress to various forms of chronic infection, including the inactive hepatitis B surface antigen (HBsAg) carrier state, chronic hepatitis, cirrhosis and HCC [1-3]. Knowledge of the natural history of hepatitis B and the risk factors of disease progression is important for developing strategies for management and therapy.

PHASES OF HBV INFECTION

The individual course of HBV infection is determined by the interaction between virus replication and the host immune response

and can be divided into four phases: immune tolerance, immune clearance, low or non-replicative, and reactivation.

In the initial immunotolerant phase, patients are hepatitis Be antigen (HBeAg)-positive. They have high serum levels of HBV DNA, but normal or minimally elevated serum alanine aminotransferase (ALT) levels and normal liver or minimal histological activity, thus indicating that the host immune response against the infected hepatocytes is lacking or minimal. After a variable period of HBeAg positivity, depending on the age at acquisition of HBV infection, immune tolerance to the virus is lost and patients may enter the immunoactive phase, characterized by fluctuating, but progressively decreasing HBV DNA levels and increased ALT and histologic activity, reflecting immune-mediated histologic damage. The third low or non-replicative phase involves seroconversion from HBeAg to its antibody (anti-HBe). This is usually preceded by a marked decrease in serum HBV DNA that is not detectable by hybridization techniques, although low levels of HBV DNA can be detected with sensitive polymerase chain reaction (PCR) assays. During this phase, referred to as the inactive HBsAg carrier state, liver disease is inactive with normal ALT and there is a subsidence of hepatic necroinflammation [1-3]. The inactive carrier state can last for decades or even for life, but in a number of patients, reactivation of HBV replication with high levels of HBV DNA and a recrudescence of liver disease occurs either spontaneously or after discontinuation of immunosuppressive therapy [4]. Reactivation of viral replication may occur due to reactivation with the wild type virus (with HBeAg seroreversion) or when replication-competent HBV variants cannot produce HBeAg because of mutations in the pre-core or core promoter regions of the core gene [5].

The low or non-replicative phase may lead to resolution of hepatitis with HBsAg loss and development of neutralizing HBs antibodies (anti-HBs) [1-3]. After HBsAg seroclearance, HBV DNA may still be detectable by PCR in serum and liver biopsy specimens, suggesting that viral eradication is seldom achieved [6]. Immunosuppression in these patients, such as during cancer chemotherapy or after organ transplantation, can lead to reactivation of hepatitis B.

CLINICAL COURSE OF CHRONIC HEPATITIS B

Persistence of HBsAg, HBeAg and high levels of HBV DNA in serum for more than 6 months after the primary infection is defined as chronic HBV infection. The proportion of patients who develop chronic HBV infection varies with age at infection; ranging from more than 90% of infants born to highly infectious HBeAg-positive mothers to less than 1% in adults, with an intermediate frequency of approximately 30% in children infected after the neonatal period but before the age of 5 [7] (Figure 1).

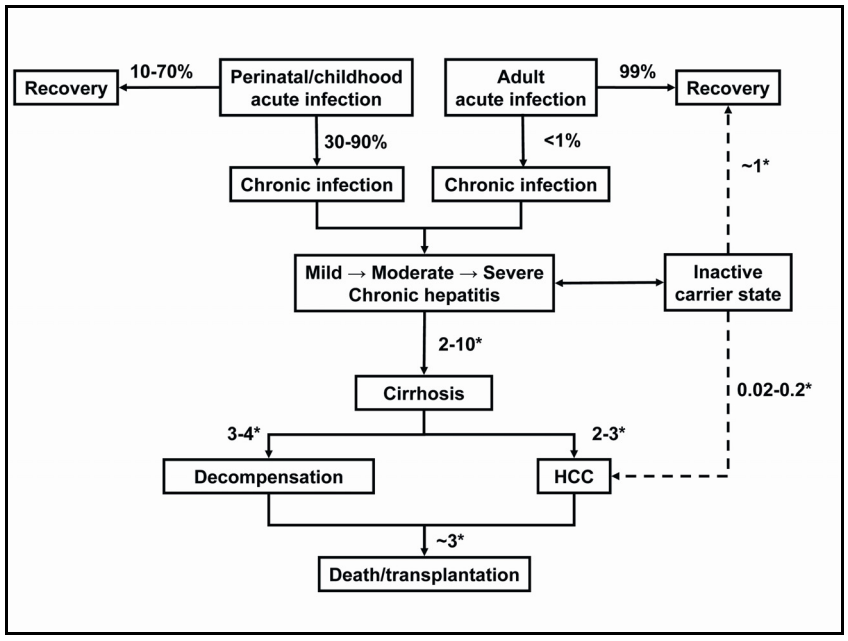

Figure 1: A diagrammatic representation of the clinical spectrum and potential outcomes of hepatitis B virus infection.
Hepatocellular carcinoma (HCC)
* incidence per 100 person years.

HBEAG-POSITIVE CHRONIC HEPATITIS B

The natural history of chronic hepatitis B is influenced by the mode of transmission and varies with regional endemicity. Perinatal transmission or infection during early childhood predominates in highly endemic areas such as Africa and Asia, where most HBsAg-positive mothers have circulating HBeAg. In low prevalence regions, such as Western Europe and North America, transmission is primarily horizontal in adolescents and adults through sexual contact and intravenous drug use.

Most Asian children with perinatally acquired chronic HBV infection, are in the immunotolerant phase when they present, with HBeAg positivity, very high serum levels of HBV DNA and mild or no liver disease (HBeAg-positive chronic hepatitis with normal ALT). The immunotolerant phase lasts 10 to 30 years and there is a very low rate of spontaneous HBeAg clearance [7]. In contrast, individuals who acquire HBV infection in late childhood, during adolescence or adulthood and become chronic carriers, usually present in the immunoactive phase with liver disease activity (HBeAg-positive chronic hepatitis).

Adult patients with HBeAg-positive chronic hepatitis usually present in the third or fourth decade of life and are more frequently males [8]. The spectrum of liver damage ranges from mild (approximately 20 to 40%) to moderate or severe chronic hepatitis (approximately 40 to 60%) or active cirrhosis (approximately 10 to 25%) [8]. Children usually show milder chronic hepatitis than adults.

Seroconversion from HBeAg to anti-HBe is a very important event in the natural history of chronic HBV infection as it is usually followed by a reduction of HBV DNA replication, biochemical and histological remission of hepatitis and a good prognosis [8-11]. The average rate of spontaneous HBeAg seroconversion has been reported to be between 8% and 15% of patients per year [8]. Factors that can affect the probability of HBeAg seroconversion include gender, age and the degree of liver disease activity. Older carriers and female carriers are more likely to clear HBeAg [12-14].

Patients with ALT levels more than 5 times the upper limit of normal (ULN) show a spontaneous HBeAg seroconversion rate of over 50% at the end of 1 year follow-up compared to less than 10% in patients with ALT levels less than 5 times the ULN [15]. Often the disappearance of HBeAg is preceded or accompanied by a transient

rise in ALT levels, known as a flare, which is the expression of a vigorous HBV-specific immune response. Although a sudden increase in serum ALT may be a favorable prognostic sign in chronic hepatitis B, some patients experience repeated episodes of flares without HBeAg loss. The clinical spectrum associated with these acute exacerbations varies greatly; patients may remain asymptomatic or develop symptoms of acute hepatitis that in some cases may progress to hepatic decompensation [13].

Recently the role of the HBV genotype on the rate of HBeAg seroconversion has been examined, but it is still uncertain. Studies from Asia have suggested that patients with genotype B tend to have a higher cumulative rate of HBeAg seroconversion than genotype C infected patients, but more recent data indicate that this difference disappears during long-term follow-up [16, 17]. There is only one longitudinal study in Western patients indicating that HBeAg seroconversion rate did not differ with different HBV genotypes [18].

HBeAg seroconversion associated with remission of liver disease reflects the transition from chronic hepatitis B to the inactive HBsAg carrier state, but longitudinal studies have shown that a proportion of HBeAg-negative patients retain or redevelop high levels of HBV DNA and persistent or intermittent elevation in ALT levels associated with liver necroinflammation and progressive fibrosis [5, 9-11]. These patients have HBeAg-negative chronic hepatitis.

HBEAG-NEGATIVE CHRONIC HEPATITIS B

The diagnosis of HBeAg-negative chronic hepatitis can be made in patients who (1) are HBsAg-positive for at least 6 months to establish chronic HBV infection, (2) HBeAg-negative and anti-HBe-positive, (3) have detectable serum HBV DNA levels by molecular hybridization techniques or by quantitative PCR assays (suggested threshold of 10^5 copies per mL), (4) elevated ALT, (5) liver necroinflammation at histology, and (6) no other concomitant or superimposed causes of liver disease [1-3, 5].

Most patients with HBeAg-negative chronic hepatitis harbor a variant virus that cannot produce HBeAg. The most common mutation preventing HBeAg production is a guanine (G) to adenine (A) change at nucleotide 1896 (G1896A) producing a stop codon (at pre-core codon 28) that prematurely terminates synthesis of HBeAg 5. Other pre-core changes as well as mutations in the basic core promoter

region which down-regulate HBeAg synthesis at the transcriptional level have been described [5]. The most common pre-core mutation (G1896A) is predominantly found in association with HBV genotype B, C and D with a thymidine (T) at pre-core position 1858. In contrast, in HBV genotype A the nucleotide 1858 is a cytosine (C) and, given the impaired base pairing between C and A, a G1896A mutation is not selected since it would diminish the replicative efficiency of HBV. Thus, HBeAg-negative chronic hepatitis is more common in Southern Europe, where genotype D predominates, and in Asia, where both genotype B and C are common. However available data suggest that HBeAg-negative chronic hepatitis is present worldwide with marked variations in the prevalence of pre-core and core promoter variants among HBeAg-negative patients in different part of the word [19].

Patients with HBeAg-negative chronic hepatitis are usually male and older than patients with HBeAg-positive chronic hepatitis (median 40, range 36-45 years) [5, 8, 20, 21]. Although the wide spectrum of histologic damage seen in HBeAg-positive chronic hepatitis may also be found in HBeAg-negative chronic hepatitis, HBeAg-negative patients are more likely to have severe necroinflammation (>50% of cases) or cirrhosis (approximately one third of cases) at the time of first clinical presentation [8, 20, 21].

HBeAg-negative chronic hepatitis has various profiles characterized by major fluctuations of both viremia and ALT (HBV DNA can fall below 10^5 copies per mL and ALT may normalize temporarily) in over 50% of patients [20]. Periods of completely normal ALT may be long lasting, but usually the disease recurs. Sustained spontaneous remissions of disease activity are rare and delayed spontaneous HBsAg loss occurs at a low rate of 0.5% [5, 11, 21].

INACTIVE HBSAG CARRIER STATE

The diagnosis of the inactive HBsAg carrier state is based on the following criteria: (1) HBeAg negativity and anti-HBe positivity, (2) undetectable or low levels of HBV DNA (suggested levels less than 10^5 copies per mL), (3) repeatedly normal ALT levels, (4) minimal or no necroinflammation, slight fibrosis or even normal liver on histology [1-3]. In patients who have already developed cirrhosis during the high replicative phase of infection, the picture in the inactive carrier state will be that of inactive cirrhosis.

Long-term follow-up studies (up to 29 years) of these carriers have shown that liver disease remains inactive in most patients, thus indicating a benign prognosis; patients rarely progress to cirrhosis or HCC [11, 22-24].

During follow-up an estimated 20 to 30% of all inactive HBsAg carriers experience spontaneous reactivation of hepatitis B with reappearance of ALT elevation and high serum levels of HBV DNA, with or without HBeAg seroreversion [4, 11]. Data indicate that HBeAg seroreversion occurs in approximately 4% of patients during 1 to 18 years of follow-up and it is often severe with a high risk of developing cirrhosis [11]. HBV reactivation is usually asymptomatic, although in some patients it may present as acute hepatitis, with or without jaundice. Intermittent or persistent reactivation of hepatitis B may be a major cause of progressive liver damage and in cirrhotic patients may lead to decompensation [4].

Spontaneous HBsAg clearance occurs during chronic HBV infection at an estimated annual incidence of 1 to 2% in Western carriers [14, 25], and even less (0.05 to 0.8%) in areas that are endemic for HBV where infection is usually acquired perinatally or in early childhood [12, 26]. The prognosis following HBsAg clearance is excellent, except in patients with cirrhosis or concomittant HCV or HDV infection before HBsAg clearance. In fact hepatic decompensation, HCC as well as liver-related mortality may still occur in patients who have already developed cirrhosis when spontaneous HBsAg loss occurs, with or without concurrent infections [25, 27].

RATES OF PROGRESSION TO CIRRHOSIS

In untreated carriers with predominantly HBeAg-positive chronic hepatitis referred to clinical centers, the reported incidence of cirrhosis ranges from 2 to 5.4 per 100 person years with a cumulative incidence of 8 to 20% over a 5 year period [8, 28, 29] (Figure 1). It has been suggested that the rate of cirrhosis is higher in patients with HBeAg-negative chronic hepatitis than in patients with HBeAg-positive chronic hepatitis, the incidence being 8 to 10 per 100 person years [11, 30, 31]. In a prospective study of patients with HBeAg-negative chronic hepatitis followed from early occurrence of the disease to after HBeAg seroconversion, the incidence of progression to biopsy proven cirrhosis was as high as 9.6 per 100 person years [11].

In adult patients with chronic hepatitis B, the average age at the time of diagnosis of cirrhosis was 41 to 52 years old (median 46) [8]. In general, progression to cirrhosis occurs insidiously and without symptoms, as indicated by a European study where only a minority (24%) of patients were symptomatic at diagnosis of compensated cirrhosis type B [32].

LIVER-RELATED COMPLICATIONS AND MORTALITY

Long-term liver-related complications of chronic HBV infection include the development of HCC, hepatic decompensation and death (Figure 1).

Hepatocellular carcinoma

The risk of HCC varies according to geographic factors, duration of HBV infection and the severity of liver disease. Indeed, there is a greater risk of HCC with chronic HBV infection from perinatal transmission in highly endemic areas than for infections acquired as an adult. In the presence of cirrhosis, the risk of acquiring HCC is correspondingly higher than inpatients without cirrhosis. In studies in countries where HBV is highly endemic (Taiwan, Singapore), the summary HCC incidence rate was 0.2 per 100 person years in inactive carriers, 1.0 in chronic hepatitis B without pre-existing cirrhosis at diagnosis and 3.2 in patients with compensated cirrhosis, with a 5-year HCC cumulative incidence of 15% in cirrhotics [33]. In Western countries where infection is slightly or moderately endemic the summary HCC incidence was 0.02 per 100 person years in inactive carriers, 0.1 in chronic hepatitis B without cirrhosis at diagnosis and 2.2 in compensated cirrhosis, with a 5-year HCC cumulative incidence of 10% in cirrhotics [33].

In a study analyzing the natural history of compensated cirrhosis type B in 161 Western European caucasian patients (EUROHEP cohort), who were delta-negative and remained untreated during a mean follow of 6 years, the 5-year cumulative HCC risk was 9% [34]. Most patients with HCC did not experience hepatic decompensation before or at the time of diagnosis of liver cancer, indicating that HCC usually develops in clinically silent cirrhosis [34].

Hepatic decompensation

The average age for the development of clinical cirrhosis is 55 years old [34, 35]. In longitudinal studies conducted in Europe [34] and Asia [36] including patients with early stages of cirrhosis (Child class A) the incidence of hepatic decompensation was 3 to 4 per 100 person years with a 5-year cumulative incidence of 16 to 20%. Overall these findings indicate that decompensation usually occurs several years after cirrhosis is diagnosed.

Mortality rates

Several longitudinal studies of the natural history of untreated chronic HBV carriers demonstrate that the mortality rate varies with the baseline clinical setting. In a series of untreated patients with chronic hepatitis B, both HBeAg-positive and HBeAg-negative, without pre-existing cirrhosis at baseline and without HDV infection, the incidence of liver-related death was low, ranging from 0 to 1.0 per 100 person years with a 5-year mortality rate of 0-1% [8, 28, 29].

The 5-year mortality rate is 14-20% in patients with compensated HBV-cirrhosis [32, 34, 37]. In the EUROHEP cohort of patients with compensated cirrhosis type B, the incidence of liver-related death was 3.5 and the 5-year mortality rate was 14% [34]. HCC and liver failure were the main causes of death. Once liver disease decompensation occurs, the prognosis is poor with the 5-year mortality rate ranging from 65%-85% [37, 38]. There is some correlation between the type of decompensation and the prognosis. The highest mortality was observed in patients with more than one complication and the lowest mortality rate in patients with ascites (62% at 5 years) [34].

PROGNOSTIC FACTORS OF DISEASE PROGRESSION

A number of viral-related, host-related and external factors may have an impact on the rate of disease progression (Table 1).

Viral-related
HBV replication status during follow-up
HBV variants
HBV genotype [a]
HDV co-infection
HCV co-infection
HIV co-infection [a]
Host-related
Age at diagnosis
Gender
Severity of liver disease at presentation
Recurrent flares of hepatitis
Sustained ALT normalization
External
Alcohol
Smoking [a]
Environmental contaminants (aflatoxin) [b]

Table 1: Factors affecting progression of chronic hepatitis and compensated cirrhosis due to hepatitis B virus (HBV).
Hepatitis delta virus (HDV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) [a] more research needed; [b] important in HBV endemic regions.

Virus-related factors

Ongoing "clinically" significant HBV replication, defined by the presence of detectable serum HBV DNA using a non-PCR assay ($>10^5$-10^6 copies per mL) or HBeAg, may accelerate the progression of chronic hepatitis to cirrhosis [20, 28, 39]. Once cirrhosis has

developed, patients with high levels of HBV replication are at increased risk of liver-related death, whereas those undergoing clearance of HBeAg, suppression of HBV DNA and ALT normalization have an improved survival rate [37, 40]. In the EUROHEP cohort of patients with compensated cirrhosis, the risk of decompensation and liver-related mortality in HBV DNA-positive patients compared to HBV DNA-negative patients was 4 fold and 5.9 fold respectively [34]. In the Dutch cohort of cirrhotic patients, loss of HBeAg and development of anti-HBe during follow-up was associated with a reduction in the likelihood of liver-related death by 2.2 fold [37]. Even in patients with decompensated cirrhosis, suppression of HBV replication and delayed HBsAg loss is an important event that may be associated with improved survival [35].

On the other hand, the prognostic role of active HBV replication at diagnosis in the prediction of HCC is still controversial. A population-based study in 11,893 Taiwanese men found that the risk of HCC increased 10-fold among men who were positive for HBsAg alone and 60-fold for those positive for both HBsAg and HBeAg at diagnosis compared to HBsAg-negative men [41]. In the EUROHEP cohort of patients with compensated cirrhosis type B, the risk of liver cancer did not differ among HBeAg-positive, HBeAg-negative/HBV DNA-positive or HBeAg-negative/HBV DNA-negative patients at diagnosis [34]. However, these negative results may be related in part to the small sample size in each group of patients and to the low overall incidence of HCC.

The influence of the HBV genotypes on the clinical outcome of chronic hepatitis B is still under investigation [42]. One study from Taiwan found that genotype C is associated with advanced fibrotic liver disease and genotype B is associated with an increased risk of HCC [43], but other studies from Japan and China reported that the life long risk of progression to cirrhosis and the development of HCC did not differ between HBV genotype B and C [17, 44] In India and the Mediterranean area, genotype D is associated with more severe liver disease than genotype A [18, 42]. Whether differences in the preferential occurrence of the pre-core and core promoter mutations in association with different HBV genotypes affect the clinical outcome of chronic liver disease has still not been clarified.

An important factor in disease progression is co-infection with similarly transmitted viral infections. The reported worldwide prevalence of serum anti-HCV in patients with chronic HBV or HDV

infection is greater than 10%, particularly among injecting drug users [45]. Co-infection with HCV and HBV or triple infection with HCV, HBV and HDV tend to aggravate the severity and the progression of liver disease to cirrhosis [45-47]. HCV or HDV co-infection in patients with cirrhosis has been linked to an increased risk of HCC [48-50].

In homosexual men with chronic HBV infection, HIV infection is associated with a lower rate of spontaneous HBeAg seroconversion and an increased incidence of cirrhosis in cases of low CD4 count ($<200/mm^3$) compared to HIV-positive patients with a CD4 count $>200/mm^3$ and to HIV-negative patients [51]. To our knowledge, no data are available on the risk of HCC in HBV/HIV co-infected persons.

Host-related factors

Older age at diagnosis appears to be an important determinant of progression to cirrhosis, HCC and increased mortality [32, 34, 37, 38, 49]. This may be because the aging immune system cannot contain the disease process or simply because of the longer duration of infection and liver disease. Fibrosis appears to progress more slowly in females than in males with chronic hepatitis B, suggesting that estrogens have a protective effect on fibrogenesis [52]. Contrasting data are available on the influence of gender on the risk of HCC [38, 53].

The biochemical and histological expression of the disease is significantly related to disease progression. The natural course of chronic hepatitis B is punctuated by spontaneous flares of hepatitis and recurrent episodes of severe necroinflammation and regeneration may increase the risk of fibrosis and cirrhosis [4, 39]. In addition, the severity of the fibrosis stage at presentation correlates with the risk of developing cirrhosis; in one study the rate of progression to cirrhosis was 0%, 6% and 17% after 5 years for stages F1, F2 and F3, respectively [29].

In patients with compensated HBV-cirrhosis, baseline clinical and biochemical characteristics that indicate decreased hepatocellular function (hypoalbuminemia, mild elevation in bilirubin levels (17-51μmol/L) and the presence of portal hypertension (decreased platelet counts, splenomegaly) correlate with an increased risk of hepatic decompensation and HCC and poor survival [32, 34, 37].

External factors

Chronic alcoholism plays a major role in increasing the rate of progression to both cirrhosis and HCC. Among patients with chronic hepatitis B, those with a history of heavy drinking have a 6 fold higher risk of progression to cirrhosis [29]. A case control study found that there was a synergy between alcohol drinking and HBV infection in the risk of liver cancer, with an increased risk of approximately 2 fold over that with alcohol alone for HBV infected subjects of both sexes who drank more than 60g/day [54]. Additional external factors that may increase the risk of liver cancer include smoking and dietary carcinogens such as aflatoxins which contaminate food stored in humid conditions [41, 55].

CONCLUSIONS

In conclusion, the difficulties of determining the natural history of chronic hepatitis B include (1) the absence of symptoms during the early stages, but also during progression to cirrhosis, (2) the slow and variable progression to cirrhosis and end-stage liver disease, (3) accompanying factors that can modify the course, including co-infections and co-morbid conditions, and (4) the now common use of antiviral treatments. At present there is no generally accepted way to predict the long-term outcome in an individual patient, although a combination of demographic, virological, biochemical, histological and environmental factors can provide useful information for describing the natural history of the disease. Further characterization of host, virus and external factors associated with rates of fibrosis progression and long-term complications of chronic hepatitis B would allow more efficient clinical management and treatment of this disease.

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