Natural history of chronic hepatitis by the hepatitis B virus

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Abstract

Chronic hepatic lesions of hepatitis may be caused by the hepatitis B virus (HBV). The prevalence of HBV infection varies widely throughout the world, from highly endemic areas in most of the developing countries, to areas of low endemicity in the developed countries. It is estimated that more than 300 million people worldwide are chronically infected by Hepatitis HBV worldwide. Chronic HBV is a major cause of death, whether by cirrhosis or by hepatocellular carcinoma. The objective of this study was to review the epidemiology, natural history and prognosis of HBV chronic hepatitis.

Key words: hepatitis B virus, chronic hepatitis B, natural history.

General information on infection and molecular biology of the hepatitis B virus (HBV)

Chronic hepatitis B is a major cause of death, whether from cirrhosis or from hepatocellular carcinoma.[1,2,3]

It is estimated that more than 300 million people worldwide are chronically infected by the hepatitis B virus (HBV), of which more than 250,000 die each year from chronic liver disease associated with HBV.[4,5]

The prevalence of HBV infection varies widely throughout the world, from high endemic areas in most of the developing countries, to areas of low endemicity in the developed countries.[5,6] In the United States and Europe, chronic hepatitis B is relatively uncommon, but it is a major cause of morbidity and mortality by liver disease.

A seroepidemiological population study recently conducted in the United States showed that 0.43% of the population was AgHBs positive, indicating that approximately one million Americans are chronically infected with HBV.[5]

HBV, identified in 1965 by Blumberg,[7] is a hepadnavirus.[8,11] Hepadnaviruses are hepatotrophic viruses which include not only the human HBV, but also the woodchuck hepatitis virus (WHV), the Peking duck (DHBV) virus and the ground squirrel (GSHV) virus.[1,11,13]

These viruses can cause persistent viral infection, but only the HBV and WHV can cause active chronic hepatitis.[12,14,15] A link between chronic HBV infection and hepatocellular carcinoma has also been established.[16,25]

The structure of the HBV virus genome was identified in 1975 by Summers et al.,[26] and defined with greater rigor in 1979, after cloning of viral DNA.[27] It is the smallest known human virus genome.[9,28] It consists of a partially double stranded circular DNA molecule.[9] The two DNA strands are of different lengths. The long chain (L) is of fixed length and, except for a short break, forms a continuous circle. The short chain (S) is of variable length, corresponding to 50% of the long chain. The circular structure of the genome is essentially given by 220 nucleotides 5' from the end of each chain; this is called the cohesive region.[28]

The length of the genome varies according to the virus subtype. The existence of subtypes whose prevalence varies by geographical location has been known for a long time.[29]

The antigenic determinant 'a', whose molecular structure is not fully known, is common to all the subtypes. Two pairs of exclusive determinants are associated with the determinant 'a', defining the classical subtypes adw, adr, ayzv, ayr.[29]

The HBV genome consists of four phases of Open Reading Frame - ORF, which are preserved in spite of the different viral subtypes, and are located in the long-chain.[11]

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The open reading phase is a coding nucleotide sequence, allowing transcription and translation of the gene.

Each of these ORF codifies for virus proteins. The different ORF jam up, thus allowing this small genome to increase its coding capacity. The four ORF of the long chain are called S-pre-S, C, P and X.[11,30]

The region S or ORFS codifies for the envelope protein that supports the antigenic determinant of surface HBs. The region S-pre-S codifies for the viral envelope proteins and is divided in regions S-pre-S and pre-S2 [28]. It is thought that the pre-S2 region plays an important role in linking the virus to hepatocytes.[31] In vitro, it has the ability to bind to polymerized human serum albumin (PHSA).[11] Similar receptors to the PHSA have been described on hepatocytes[32] and are specific to human albumin. Its terminal N sequence codifies for the pre-S2 region and contains a dominant epitope located on the surface of the envelope. It is believed that it induces the appearance of neutralizing antibodies, inhibiting the direct binding of the virus to the hepatocyte membrane, and it probably plays an important role in linking the virus to the hepatocyte.[33]

The pre-S2 antigen is a good viral replication marker[34], which is correlated with the amount of HBV DNA and is present, whatever the status, in the HBe system. The pre-S1 sequence is essential for recognition of the hepatocyte receptor.[11]

Chronic hepatitis is a chromium liver injury characterized by infiltration of portal spaces and periportal areas by mononuclear cells (lymphocytes), necrosis of limiting lamina hepatocytes, and portal and periportal fibrosis. In more severe forms, these three injuries penetrate the interior lobe, toward the centrilobular vein, creating a bridge design that extends from the portal areas to the central lobe vein. Over the long term, chronic hepatitis can lead to the development of cirrhosis.[35-37]

The arguments in favor of chronic hepatitis by HBV are as follows:[3,35,38,39] (a) presence of HBsAG in serum; (b) presence of serum markers of viral multiplication (HBeAg and/or HBV DNA); and (c) absence of anti-Delta anti-bodies.

The incidence of chronic HBV carriers with chronic hepatitis is twenty to thirty new cases per million per year in Western European countries (countries with low endemicity).[35] Less than 10% of the population find HBV at the end of their life. The contamination is concentrated in certain high risk groups[5, 35, 40-41] mainly health care professionals, individuals who have received blood transfusions (especially hemophiliacs and haemodialysis patients receiving anti-hemophilic factor), male homosexuals, drug addicts, and individuals living in the household of a chronic HBV carrier.[38] However, despite the negative HBeAg, twenty to ninety percent of these patients are positive for HBV DNA in the blood serum and the appearance of HBcAg in the liver. The persistence of HBV replication in patients with HBeAg negative chronic hepatitis is usually associated with severe liver disease and a poor prognosis.[42,43]

Natural history of HBV chronic hepatitis

Cirrhosis is the consequence of prolonged hepatocytes injuries, whatever the cause. The destroyed hepatocytes lead to the development of excessive quantities of fibrous tissue; this results in regeneration of the remaining hepatocytes; due to fibrosis, this regeneration does not lead to the constitution of normal lobes, but the formation of nodules. Cirrhosis is a diffuse process.[35,37,44,45] In two thirds of chronic patients, the liver is either normal or the site of limited and stable lesions in these patients, and the risk of subsequently developing cirrhosis is low.[35] On the other hand, in one third of chronic patients, the liver is the site of chronic hepatitis, with a risk of subsequent development of cirrhosis.[35]

In the course of chronic infection, HBV is not cytopathogenic.[35,46,47] The hepatocyte lesions caused by chronic infection are the consequence of the cellular immune response directed against the hepatocytes presenting viral antigens on their surface (it is thought that the antigen against which the immune response is directed is HBcAg).[35, 48, 50]

The natural history of chronic infection by VHB[30, 35,37,51,58] consists of three successive phases (*Table 1, Fig. 1*), serving the relationship between the level of viral replication and the histological activity.

In the first phase (active viral multiplication), which lasts from one to several years, there is a source of HBV multiplication, translating as an insufficient immune cell response, where the destruction of the hepatocytes is moderated. The serum markers, reflecting the multiplication of the HBV (HBeAG and HBV DNA), are present in the serum[35,59,60,] in a high percentage. All the histological levels reached can correspond to this phase.[59, 61, 62]

TABLE I

Characteristics in the biology, serology, histology and infection of chronic hepatitis by the hepatitis B Virus

	High replication Stage	Low replication Stage	Non replication stage
Ag Hb[a]	+	+	+
Ag HBee	+	+/-	-
Anti- HBee Ab	-	-/+	+
DNA-HBVd	+	+/-	-
Serum ALT	↑	N or ↑	N or ↑
Liver Inflammation	Present	Minimum	Absent
Infectiousness	+	Minimum	Nihil

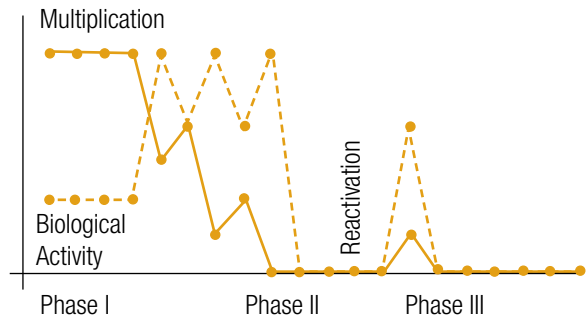
[a] AgHBs = HBV surface antigen; b HBV "e" antigen; c anti-HBe = HBV "e" antigen antibody; d = HBV desoxyribonucleic acid

In the second phase (serum conversion or immune clearance phase,)[35, 59, 61] which lasts from a few weeks to a few months (sometimes one to two years), the immune response becomes more vigorous and as a result, the viral multiplication slows down. In this phase, the destruction of the hepatocytes is more visible[58,59] and there are severe lesions from chronic hepatitis.[59] The patient becomes less contagious than in the previous phase.[59,63]

In the third phase (viral inactivation phase), the viral multiplication is interrupted, but the viral genome has been integrated in the host genome.[25,51,44, 63] There are no complete viral particles in the serum. The destruction of the hepatocytes is small, because the HBcAG, not being synthesized, no longer appears at the surface of the hepatocytes.[35,64] The activity of the hepatic lesions is small or null.[59] The patient is only slightly, or not at all contagious in this phase. The risk of hepatocellular carcinoma at this stage of HBV infection is especially high if there is cirrhosis[36] and the patient is male.[35]

During the third stage, there may be reactivation periods[53,55,59,66-69] lasting from several weeks to several months, during which viral multiplication restarts.[70,71] These may produce hepatic lesions that are more, or less severe. The patient then becomes highly contagious.[71]

The prognosis of active chronic hepatitis by HBV is severe.[35,45] In most cases, after an interval of 10 to 40 years after the initial infection, hepatic cirrhosis develops.[35,59] Furthermore, twenty percent of patients suffering from cirrhosis are at risk of hepatocellular carcinoma.[23,35,72]



Natural history of chronic hepatitis B. During the first phase, hepatitis activity is low and viral multiplication is high. During the second phase, hepatitis activity increases and viral multiplication slows down. During this phase, there may be episodes of exacerbation of chronic hepatitis (seroconversion hepatitis). During the second third, the chronic hepatitis activity disappears, as well as the viral multiplication. During this phase there may be episodes of reoccurrence of chronic hepatitis.

FIG. 1

Three HBV serum markers have been used as indicators of active viral replication: HBeAG, HBV DNA and HBV DNA polymerase. At present, the most sensitive replication marker is HBV DNA.[38, 73-75] This HBV replication marker is more specific and more sensitive than the HBeAG and the DNA polymerase. The HBeAG indirectly measures HBV replication, since it circulates in the form of a soluble protein, independent of the viral particles.[76, 77]

The presence of HBV DNA in chronic hepatitis B was compared, in particular, with HBeAg, although in heterogeneous groups,[38, 75, 78-80] in other studies, the

prevalence of HBV DNA was compared to other viral replication markers such as intracellular HBcAg[81, 84,] and the activity of DNA polymerase.[38, 85] The prevalence of HBV DNA in patients with HBeAg varies from 80% to 100%. The correlation with the activity of DNA polymerase is good,[38,85] with detection of intracellular HBcAg[82,84] and increased transaminases. When the serum concentration of HBV DNA is high, the HBcAg is located primarily in the nucleus and sometimes, in the cytoplasm, and it is also intranuclear when the HBV DNA is more weakly positive.

With regard to histological activity, there is an especially good correlation between the lobular activity and blood serum HBV DNA[62,63,86], while the correlation with periportal inflammatory activity is less satisfactory.[86] On the contrary, when there is hepatic cirrhosis associated with chronic hepatitis in an HBeAg positive patient, the prevalence is lower, ranging from 43% to 54%.[87] It is customary to observe, in patients who are HBeAg positive and HBV DNA negative, rapid seroconversion of HBeAG antibodies into anti-HBe antibody.[75, 88]

Various authors[43, 79, 89-91] have studied the patients with anti-HBe antibody. The majority of these patients are chronic carriers of HBsAg and have no circulating viral DNA. In these cases, the DNA polymerase is usually absent from the serum[42] and intracellular HBcAg is not present. [42, 92] However, a certain number of patients with anti-HBeAb and chronic liver disease are also carriers of HBV DNA,[42, 43, 76, 87, 92] in which case, the DNA polymerase is also not detected,[92] and the intracellular HBcAg is present or absent.[42, 84]

Typically, in regions where HBV infection is acquired during adulthood, particularly in the West, there are close links between the presence of HBeAg and HBV DNA.[87] On the other hand, in Southern Europe, Southeast Asia and Africa, regions where the infection is acquired in the neonatal period or during childhood, there is disagreement with the results observed in Northern Europe, often with the presence of anti-HBeAb associated with the presence of HBV DNA.[52, 78, 87]

Recently, various authors[43, 93-95] have shown, in patients of Mediterranean or Asian origin, that it is possible to simultaneously detect the HBV DNA Ab and the anti-HBe in the serum. This particular situation is linked to the appearance of a modified nucleotide, determining the existence of a codon stop TAG in the carboxy terminal end of the pre-C region, thereby preventing synthesis of the HBeAg. This form of hepatitis is usually more severe and progresses more rapidly to cirrhosis.[43]

The HBV DNA is not detected if the Ac anti-HBc is the only serum marker present or, else it is only detected in rare cases.[59] Similarly, in patients with the anti-HBc and anti-HBs antibodies, the HBV DNA is not detected, except perhaps in immunocompromised patients,[96, 97] where it may be present in about 10% of cases.

Reactivation of viral replication has been described in patients with HBsAg.[55, 66, 98, 100] This reactivation may be spontaneous, or related to decreased cellular immunity.[66,100] The reactivation is sometimes associated with elevated transaminases or symptoms mimicking acute viral hepatitis.[99,101] In many cases, reactivation is evident because it is accompanied by the reappearance of serum HBeAg and is not therefore a true diagnostic problem.[99,101] However, in some cases, the patient remained seropositive for anti-HBeAb and the reactivation is only marked by the reappearance of HBV DNA in the serum.

It is assumed that the persistence of Ag HBe is associated with persistently high levels of transaminases and the development of severe histological injuries, whereas antigen seroconversion in anti-HBe antibody is followed by a decrease in biological activity and histological disease.[35,54] Similarly, clearance of circulating HBV DNA is associated with normalization of transaminases in most patients in whom chronic hepatitis B is not complicated by infection D.[59]

There are also, as we have seen, patients who are seropositive for HBV DNA and anti-HBeAc: these patients have significantly elevated transaminase levels and severe histological lesions,[43,89] in contrast to those who are negative for HBV DNA and are in the chronic carrier stage. These results suggest that the presence of HBV DNA has significant prognostic value, regardless of other markers.

Bonino et al.[42] have shown that patients who are seropositive for anti-HBeAc and HBV DNA progressed towards chronic hepatitis, while in individuals who seronegative for HBV DNA, the transaminases were normal. On the contrary, active viral replication, indicated by the presence of HBV DNA, is not always associated with important histological activity.[59]

Chu et al.[52] have demonstrated that such patients had, at first, immune tolerance to the HBV (which can progress to the immune clearance phase, cha-

racterized by decreased concentration of HBV DNA), linked to immune destruction of hepatocytes, the site of active replication of HBV.

In the course of chronic hepatitis B, the presence of HBV DNA is therefore directly correlated with HBeAg. In the evolution of the disease, HBV DNA clearance precedes or coincides with the usual HBeAg, but, in some patients, HBV DNA may remain in the serum for a limited period, while the Ac anti-HBe is already detectable. In addition, the serum HBV DNA remains detectable in a variable number of patients who are seropositive for HBsAg and anti-HBeAc. This profile is mainly observed in geographic regions where HBV infection is endemic.[89]

In patients who are seropositive for HBeAg, research by CRP of HBV DNA in the blood serum is always positive.[102] Furthermore, the HBV DNA is often highlighted by CRP in patients who are seropositive for anti-HBeAc (up to 70% of cases).[102]

The control and eventual elimination of transmission of infection by HBV are possible with the proper use of vaccines.[103] The prevention of chronic infection has the potential advantage of reducing the association between chronic liver disease and hepatocellular carcinoma. Strategies for effective use of the hepatitis B vaccine have been developed worldwide, and are being implemented in areas where vertical transmission is the predominant source of infection. Unfortunately, most infections occur among adults to whom access is difficult, and who acquire the infection before they realize that they constitute a risk group. The epidemiology of HBV infections is constantly shifting among various risk groups, which reinforces the need for vaccination. The overall approach to this problem, which would seek to eliminate HBV, should be directed against infections acquired during youth. The epidemiology of HBV infections in the United States[6] indicates that transmission of this infection can be eliminated.

Chronic hepatitis B and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) develops from hepatocytes, and is one of the most common cancers worldwide.[113,114] The annual incidence per 100,000 individuals is one to five in Western Europe.[35] The cancer affects mostly men (80% to 90% of cases) aged 40 - 50 years older.[18,35] In most cases, the extratumoral liver is cirrhotic[19,23] and hepatocellular carcinoma develops 20-40 years after initial infection in patients in whom viral multiplication was almost always interrupted.[35] About 10% of infected individuals become chronic HBV carriers.[35] Chronic HBV infection plays a fundamental role in the etiology of hepatocellular carcinoma.[25,65,113,115-118]

Most hepatocellular carcinomas occur during the course of liver cirrhosis.[25,65,113,116] Chronic hepatitis B is a major risk factor for the development of HCC associated with cirrhosis. Marcellin et al.[23] identified sequences of HBV DNA in the liver of most patients with HCC and cirrhosis in France, including patients who were seronegative for HBsAg.

In the Philippines, hepatocellular carcinoma is one of the most frequent malignant tumors in children aged between 5 and 14 years of age[16]: with the virus subjected to a short incubation period and fewer children being exposed to environmental carcinogens during youth, CHC is therefore a good model to study the carcinogenic potential of HBV.

A close relationship exists between HBV and HCC, documented in clinical, epidemiological and Molecular Virology studies.[16-25,116,119-122]

Molecular Virology studies have demonstrated the integration of HBV DNA in the HCC tissues.[65,117] These studies have been conducted mainly in adults. There seems to be a unique model of integration in the children studied with HCC[16] which is a good model of carcinogenesis. The most preserved fragments in the integrated HBV genome were fragments containing the gene for surface antigen and gene X.

HBV is also the most important determinant of HCC in almost every country in the world, the risk being 10-100 times higher for carriers of HBsAg, compared with non-carriers.[120,121] Marcellin et al.[23] found a low incidence of HBV serum markers of liver HBV DNA in patients with HCC developed in histologically normal liver. Lai et al.[21] conclude that a substantial proportion of patients who were seronegative for HBsAg and seropositive for anti-HBsAb with chronic liver disease and hepatocellular carcinoma had sequences of HBV DNA in the liver, and that integration may play a role in the development of hepatocellular carcinoma. Lok et al.[22] also demonstrate that despite the long interval between the onset of hepatitis B and development of HCC, the HBV replication persisted in the majority of patients with HCC, although at low levels. However, there is a marked difference in the incidence of HCC in males

and females, despite similarities in the prevalence of HBsAg in both sexes. This suggests the possible role of the hormonal milieu, and also environmental factors, such as drinking alcohol and smoking. A study by Kalayci et al [19] confirmed that HBV infection is more often associated with HCC in the presence of cirrhosis, although there is also a high incidence of HBV infection in the absence of cirrhosis.

There appear to be two mechanisms of carcinogenesis:[65] direct and indirect. Viral carcinogenesis begins with the integration of HBV DNA at the genomic DNA of the host cell (direct mechanism), with deletions and translocations of small amounts of viral DNA. The consequence is necrosis and inflammation (indirect mechanism) that will act as promoters of carcinogenesis. The necrosis and inflammation determine the onset of mitosis, which will be a possible factor promoting HCC. Chronic carriers of HBsAg are at greater risk of developing HCC than individuals who are immune to HBV or are not infected. Neoplastic transformation generally requires a promotional factor, such as anarchic growth and clonal expansion of the liver cells.

However, whatever the pathogenic mechanism, it involves a long history of active replication of HBV, as well as necro-inflammation in the presence of cirrhosis.[123]

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