Is HBV genotyping of clinical relevance ?

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Abstract

The hepatitis B virus, as is the case of the hepatitis C virus, can be categorized in several genotypes. The genotyping of HBV is based on the nucleotide sequence divergence encoding the amino acids constituting the HBV surface proteins. Since the genotype of the hepatitis C virus is shown to be related to epidemiology and response to interferon therapy, one wonders whether this also holds for the hepatitis B virus. HBV genotypes clearly are found to be different in various geographical areas of infection. In Europe, genotypes A and D are predominant, whereas in Asian patients genotypes B and C are more frequent, and in the Middle-East the genotype D. Data concerning the clinical relevance are less clear but it seems that in Europe, the genotype A has a higher HBeAg clearance rate and a better outcome. In Asia, genotype B (and especially the genotype Bj) is associated with a higher HBeAg clearance and with less development of cirrhosis and HCC. The impact on spontaneous or therapy induced viral resolution is not yet clearly identified. Further evaluation in different countries is needed to delineate the impact of the genotype relative to other factors such as age at infection, level of serum transaminases and viral load, on the course of infection, complication, outcome of treatment and prognosis. (Acta gastroenterol. belg., **2005**, 68, **233-236**).

Key words : hepatitis B, genotypes, treatment.

Introduction

Genotyping of the Hepatitis C Virus (HCV) is nearly a routine procedure since it carries information with regard to the epidemiology and the mode of infection and since it has an important predictive value as to the efficacy of interferon therapy. HCV is an RNA virus with at least 6 genotypes, defined by a sequence diversity of more than 20%. Genotypes 1, 2 and 3 are the most prevailing types in Europe and the USA, whereas genotype 4 is the genotype most often seen in North and Central Africa and in the Near and Middle East. The response to treatment with peggylated Interferon and ribavirin is 40- 50% for genotype 1 but > 80% for genotypes 2 and 3 (1,2).

The Hepatitis B Virus (HBV), a DNA virus, has also recognized genotypes, but it is only recently that one is looking for clinical relevance. It is the aim of the present text to overview the current state of this issue (Table 1).

Structure of HBV and HBV genotypes

Following infection of a given individual, the virus enters the hepatocytes and viral genes replicate and induce formation of the various viral proteins which are assembled for virus production in the hepatocyte (Figure 1).

Table 1. — **HCV compared with HBV**

	HCV	HBV
Virus	RNA	DNA
Genotypes	1, 2, 3, 4, 5, 6	A, B, C, D, E, F, G,H
Most prevailing types in Europe	1, 2, 3	A, D
Sequence heterogeneity	≥ 20%	≥ 8%
Response to treatment with IFN and ribavirin	30-40% : type 1 70-80% : type 2, 3	?

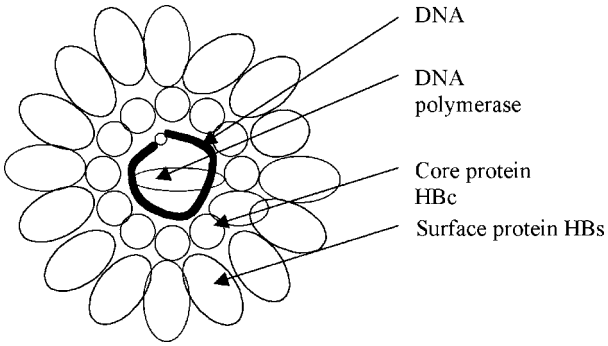

Figure 1. — Schematic representation of HB virus structure

Mutations can occur during the replications of the virus. Most well recognized are the precore mutation leading to the HBe Ag negative precore HBV mutant, and this virus is quite frequently found in the Mediterranean area. Mutations also occur in the genes coding for the HBs and pre-S proteins. This leads to a heterogeneity of the surface proteins. When this heterogeneity is quite pronounced (per definition when 8% or more of the HBs nucleotide sequences differ from another HBs Ag), one refers to it as to another genotype. These different genotypes result in formation of different HBs proteins, previously known as serotypes adw, ayw, adr and ayr, as based on antigenic determinants of HBs Ag (Table 2).

Currently 8 genotypes are recognized for HBV : genotypes A, B, C, D, E, F, G and H. In addition the genotype B has recently been subdivided into 2 subgroups : HBV-Bj, found in Japan, and the HBV-Ba, documented in the other Asian countries (3). HBV-Ba

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Table 2. — **Geographical distribution of HBV genotypes and serotypes**

HBV genotypes	HBsAg serotype	Distribution areas
A	adw2, ayw1	Northwest Europe, North America, Central Africa
B	adw2, ayw1	Indonesia, China, Vietnam
C	adw2, adr-, adrq+, ayr	East Asia, Korea, China, Japan, Polynesia, Vietnam, Asians in USA
D	adw2, ayw3	Mediterranean Area, Turkey, Middle East, India
E	ayw4	Africa, subsahara
F	adw4q-	American Natives, Polynesia
G	adw2	United States, France
H		Central and South America

seems to be a recombination of HBV-Ba with genotype C in the precore and core region. The prevalence and predictive value of HBV genotypes will be discussed below.

HBV genotype and geographical occurrence

The HBV genotypes have been found different in various geographical localization. In Europe the most occurring genotypes are A and D, and less frequent F and G (Table 2). Genotype D is nearly the only one found in Turkey (4) and in the Middle East area. The genotypes B and C are predominant in Asian countries. In the United States, because of the ethnic diversity, there are different variations of important genotype-groups. However, in a nationwide study (5) in the United States genotypes A and C were found most common.

HBV genotype and clinical evolution

A Swiss study (6) investigated the prevalence of HBV genotype A and D in 30 patients with acute resolving hepatitis B compared to 35 patients with chronic hepatitis B. They observed that 24 of the 30 patients (80%) with acute hepatitis B had the genotype D whereas in the chronic hepatitis group only 4 (11%) had type D but 28 of the 35 patients (80%) had genotype A. Thus, genotype A was more associated with chronic disease while genotype D was predominant in acute hepatitis. This was independent of age, gender and duration of the chronic disease. A study of 258 patients with chronic hepatitis B from Barcelona (7) revealed a prevalence of the genotype A, D, F of respectively 52%, 35% and 7%. Biochemical and virological remission during follow up occurred in 43% (nearly half induced by interferon, spontaneously in the others). Seroconversion of HBe Ag to anti-HBe occurred in 60% of the patients with the highest prevalence in genotype A (55%) compared to genotype D (26%) or F (26%). HBV A genotype was thus more frequent and was associated with a higher rate of biochemical and virological remission, a higher HBe Ag seroconversion and a higher HBs Ag clearance. This latter outcome of genotype A was only clear after approximately 2 years of follow up (Table 3).

An American study with 269 patients, all of Chinese origin, documented HBV-B in 44.7% and HBV-C in 53.9%. Follow up showed that genotype B was associated with a higher incidence and a more rapid HBeAg seroconversion rate (8). Age above 30 years and an initially elevated ALT were other positive predictive factors. Similar results were obtained in a Japanese study (9) of 585 patients with chronic hepatitis (Table 3), but a significant difference was only noted in patients below 46 years of age. A Chinese study (10) observed a diversity of genotypes A, B and C, but with a predominance of HBV-C of 81.4%. HBeAg positivity was highest in genotype C. Outcome was worst in patients with HBV-C genotype. Similarly, a study from Japan by Nakayoshi *et al.* (11) showed a higher clearance of HBeAg, even within 2 years, in genotype B than C ; respectively 61.5% versus 7.1%, while the development of cirrhosis was lower in genotype B than in C : respectively 11.4% versus 32.4%.These findings suggest that HBV-C genotype is associated with more severe disease, and a lower clearance rate of HBeAg than genotype B.

HBV genotype and complications

Kao *et al.* (12) revealed earlier in a study including 270 Taiwanese patients of whom 53% had HBV-B genotype and 32% HBV-C genotype, that the prevalence of genotype C was higher in patients with cirrhosis and in the elderly ($\geq$ 50 years) with hepatocellular carcinoma (HCC), whereas in contrast, genotype B was more often present in younger patients with HCC. This last finding was in contradiction with a Japanese study (9) where the HBV-B genotype was found more frequently in older patients with HCC. This finding was confirmed in a geographical study of genotypes B and C in Japan, where the mean age of HCC with HBV-B genotype was older than in those with HBV-C genotype (13).

Probably the difference in subgroup Ba and Bj, respectively in the Taiwanese and Japanese patients, is responsible for this difference, but no information was collected on the subdivision in 2000. Another Japanese study (14) documented a predominance of HBV-C genotype in chronic liver disease, in cirrhosis and in HCC in patients younger than 50 years, but in those older than

Table 3. — **Chronic liver disease : Cumulative rate of HBe seroconversion by genotype**

In Europe :

	2 years	4 years	6 years	8 years	10 years
Genotype A	0.20	0.40	0.50	0.58	0.62
Genotype D	0.12	0.20	0.25	0.26	0.30
Genotype F	0.20	0.22	0.28	0.28	0.28

Data adapted from ref 4.

In Asia :

	2 years	5 years	10 years
Genotype B	0.55	0.78	0.80
Genotype C	0.22	0.42	0.60

Data adapted from ref 6.

50 years there was no significant difference between genotype B and C.

Sanches-Tapias *et al.* (7) studied chronic hepatitis and the long term outcome. They found more complications such as hepatic decompensation and death with HBV-F than HBV-D. In the nationwide study of the United States genotype B was less associated with decompensated cirrhosis (5).

HBV genotype and therapy

Another study from Kao *et al.* (15) in Taiwanese patients, all with chronic hepatitis and treated with interferon-alfa therapy (5 MU, 3 times a week during 24 weeks), showed that genotype HBV-B was associated with a higher biochemical and virological response rate than HBV-C. Here to, the positive predictive factors for response to IFN-alfa therapy were HBV-B genotype and the younger age of the patient, whereas genotype C and the presence of the core promoter mutant (G1764A-mutation) were negative factors. An American study (16) compared treated and untreated chronic hepatitis patients and revealed a significantly higher seroconversion induced by treatment in both B and C genotypes, but genotype B still fared better than genotype C.

Chien *et al.* (17) showed that different genotypes may respond differently to lamivudine therapy. Patients with the genotype B have a higher sustained HBeAg-clearance after treatment than genotype C ; respectively 61% versus 25%. Lamivudine resistance due to development of the YMDD mutation seems independent of genotypes, but there is a higher incidence of lamuvidin resistance in patients who are HBeAg positive than those who are HBeAg negative, and since the genotype C is associated with a lower HBeAg seroconversion rate, the genotype might indirectly be involved in lamivudine resistance. However within the genotype B group, Akuta *et al.* (18) found a higher resistance to therapy in the Ba subtype than in the Bj subtype. Treatment of chronic hepatitis B eAg negative patients in Taiwan demonstrated a slightly higher relapse rate 12 months after withdrawal of lamivudine in genotype C compared to B, but the pre-treatment serum HBV-DNA level was the most important decisive factor (19). A recent study by Zolnner *et al.* (20) from Hamburg investigated viral differences between HBV genotype A and D of lamuvidin resistant chronic hepatitis. They showed different patterns of resistance-associated mutations in genotype A and D during lamuvidin treatment. This means that a genotype may have impact on treatment and outcome.

Conclusions

In reviewing recent data on HBV genotypes, it is clear that HBV genotypes are found different in various countries according to the geographical area of infection. In Europe, genotypes A and D are predominant, whereas in Asian patients genotypes B and C are prevalent. Data concerning the clinical relevance are less clear, because most of the study populations are too small, but it seems that in Europe, the genotype A has a higher HBeAg clearance rate and a better outcome. In Asia, genotype B (and especially the genotype Bj) is associated with a higher HBeAg clearance and with less development of cirrhosis and HCC. The impact on spontaneous or therapy induced viral resolution is not yet definitively identified. Further study and evaluation in different countries is still needed to delineate the impact of the genotype relative to other factors such as age at infection, level of transaminases, of viral load etc.

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