Patients were HBeAg-positive. Genotype A was almost exclusively represented, 71.2% were Caucasians, 15.8% Africans, 13.0% Asians. Fifty-seven patients (36%) were HIV-infected. Eighty-two (42.3%) were HBeAg-positive. The genotype A was more frequently associated with HBeAg-positivity than genotype D with HBeAg-negativity. Genotype A was more frequently associated with HBeAg-positivity and genotype D with HBeAg-negativity.

Introduction

Chronic hepatitis B virus (HBV) infection remains a major public health problem worldwide with approximately 300 million chronic carriers and the development of severe complications such as liver cirrhosis and hepatocellular carcinoma [1]. The course of HBV infection depends on several factors modifying the immune response, including age at infection and host genetic factors [2], and it probably also depends on the genetic variability of the virus, which influences the expression of viral antigens. Indeed, HBV replicates via a reverse-transcription step and is estimated to have a high mutation rate [3]. On the basis of a comparison of complete genomic sequences, seven major viral genotypes, designated A to G, have been identified and correspond to viral isolates sharing more than 80% homology in their nucleotide sequences [4-7]. HBV genotypes have distinct geographical distributions. Genotype A is found in North America [4] and Northern Europe, as well as in parts of Africa [8, 9].
while genotypes B and C are the most common in Southeast Asia [4]. Genotype D is found universally [8]. Genotype E is predominantly found in Africa [8], and F clusters in Central and South America [10]. Genotype G has been reported in the United States and France [7].

Accumulating evidence suggests that HBV genotypes have an impact on the pattern of mutations in the pre-core (PC) and core (CP) regions, the natural course of chronic HBV infection [11-15], or the severity of underlying liver disease [16, 17]. Genotypes B and C have been studied most extensively due to their co-circulation in Asia, allowing differences in ethnic or racial background of the patients. These studies have shown that genotype B, compared to genotype C, is associated with a higher rate of seroconversion from HBeAg to anti-HBe antibody, less active liver disease, and a lower rate of progression to cirrhosis. Correspondingly, genotype C is more prevalent among HBeAg-negative patients than genotype B. This pattern is similar, compared to genotype D, genotype A is more prevalent in HBsAg-positive than in anti-HBe-positive antibody patients. Several studies indicate that HBV genotypes may be associated with differences in treatment response [18-20]. Genotype C is associated with a lower response rate to alpha interferon therapy compared to genotype B. In Caucasian patients, a better response to peginterferon alpha-2b and lamivudine was found when patients were infected with genotype A vs genotype D. Investigating the clinical significance of HBV genotypes is becoming increasingly relevant. The identification of HBV genotypes could be useful to monitor HBV infection and related diseases and may also help in implementing appropriate therapeutic regimens.

To date, there are little data on the prevalence and clinical significance of HBV genotypes in France. One previous study suggested that HBV genotypes A and D were predominant in this country and that genotype A was associated with HBeAg positivity, while genotype D was associated with HBsAg negativity [21]. Another study by Ganne-Carrié et al. concluded that HBV genotypes A, B, C, D, and E circulated in the Seine-Saint-Denis District, close to Paris, reflecting the multiple geographical origins of patients [22].

The aim of this study was to determine the prevalence and distribution of HBV genotypes among a consecutive sample of patients with HBV infection with or without HBV coinfection in Bordeaux (France) that caters to patients from various parts of Southwestern France. Additional objectives were to determine whether there was an association of HBV genotypes with patients demographics, clinical status, and PC and CP variants.

Materials and methods

Patients

Patients with HBV infection and referred to our virological laboratory (Pellegrin hospital, Bordeaux, France) from different clinical departments between November 1999 and May 2004 were retrospectively and systematically included in the survey. The inclusion criteria were a serologically proven chronic HBV infection (HBsAg positivity >6 months), HBV DNA positivity with concurrent HBeAg, and anti-HBe tests. Patients with HBV positivity or HBV treatment were also included.

Clinical findings

Information relating to the patients’ demographics, clinical and virological status and hepatic disorders (clinical, biological and histological) were recorded anonymously and retrospectively from the patients’ medical files. Whenever a treated patient had a liver biopsy, it was performed before treatment. In HBV infected patients, epidemiological, clinical, biological and therapeutic data were retrieved from the ANRS CO3 Aquitaine cohort database of the Group Epidemiologie Clinique du Sida en Aquitaine (GECASAI) [21]. Epidemiological characteristics included sex, age, and ethnicity. Coinfection with the immunodeficiency virus (HIV), the hepatitis C virus (HCV), and the delta virus (HDV) were also recorded. The presumed source of HBV infection was determined by inquiring about the patients’ sexual behaviour (intercourse with an HBV contaminated sexual partner), history of intravenous drug use at least once, blood transfusion, vertical transmission (HBsAg-positive mother), iatrogenic exposure (endoscopic or coelioscopy examination, history of surgery, acupuncture, hemodialysis).

Detection of virological markers in serum

The study population was tested routinely for HBeAg, HBsAg, and anti-HBe antibody (Dade Behring Laboratories, Marburg, Germany), HBV antibodies (Dade Behring, Marburg, Germany), HCV antibodies (Coho Clinical Diagnostics, Rantain, NL), and anti-delta antibodies (DiaSorin, Saluggia, Italy).

Determination of HBV genotypes and detection of PC stop codon (G1896A) and CP variants (A1762T, G1764A)

HBV DNA was extracted from 200 µL of serum using QIAamp DNA blood mini-kit (Qiagen, Hilden, Germany). HBV genotyping was performed by sequencing the core and polymerase region. Two rounds of polymerase chain reaction amplification were used for polymerase region studies [24]. The first round used primers CHBV-1 (5'-CCGCAGTGCTCTCCGAGTTG-3') and HBV17 (5'-GCCGCGGAGAAGGATGACGTT-3') nested polymerase chain reaction using primers VT301 (5'-CTGGAC-CWANNARTGAGACCTCC-3') and VT102 (5'-GCAAAANCCAAAGGA-CAAATT-3') yielded a 721-bp DNA fragment encoding part (nt 1214-1934, subdomains A-E) of the HBV DNA polymerase gene. Amplification of the reverse sequence was performed by nested polymerase chain reaction as previously described [25]. The following primers were used for the amplification of the reverse region (nt 1,814 to 1,900) and the core promoter (nt 1,742 to 1,849 of the HBV genome. The external primers were 5'-CAGCGAGGAGACTTCCTGACT-3' (sense, nt 1,651 to 1,672), and 5'-GCCGCGGAGAAGGATGACGTT-3' (antisense, nt 2,394 to 2,369), and primers laminar 2 round PCR were 5'-CAACGACCGACCTTG-3' (sense, nt 1,679 to 1,698) and 5'-AGC- TGTCACGAGAGGTAGAAGG-3' (antisense, nt 1,783 to 2,009).

The amplified PCR products were purified by the QIA quick PCR purification kit (Qiagen) and then used for direct sequencing using internal antisense primer. Sequencing of the purified products was conducted by sequencing a part of the polymerase region. Two rounds of polymerase chain reaction were used for polymerase sequence analysis. The first round used primers CHBV-3 (5'-CCTGCTGGTGAGCCCTGACCC-3') yielded a 721-bp DNA fragment encoding part (nt 1214-1934, subdomains A-E) of the HBV DNA polymerase gene. Amplification of the reverse sequence was performed by nested polymerase chain reaction as previously described [25]. The following primers were used for the amplification of the reverse region (nt 1,814 to 1,900) and the core promoter (nt 1,742 to 1,849 of the HBV genome. The external primers were 5'-CAGCGAGGAGACTTCCTGACT-3' (sense, nt 1,651 to 1,672), and 5'-GCCGCGGAGAAGGATGACGTT-3' (antisense, nt 2,394 to 2,369), and primers laminar 2 round PCR were 5'-CAACGACCGACCTTG-3' (sense, nt 1,679 to 1,698) and 5'-AGC- TGTCACGAGAGGTAGAAGG-3' (antisense, nt 1,783 to 2,009).

For genotype characterization, all sequences were compared to at least 24 Genbank sequences representative of all known HBV genotypes.

Statistical analysis

Quantitative variables are described by their mean and range, and categorical variables by percentage. Comparisons between patients who were performed using Kruskall Wallis non-parametric test for quantitative variables and Fisher’s exact test for categorical variables. Multiple logistic regression with forward stepwise analyses were used to determine the independent factors associated with HBV genotypes A and those associated with HBV genotypes D. The variables related to genotype A and genotype D with P<.10 in univariate analysis were entered into the logistic model. Results were considered statistically significant at P<.05. Data were analysed using SAS version 8.2 software package (SAS Institute Inc., Cary, NC, USA).

Results

At total, 194 patients (152 males and 42 females) were identified and enrolled. Their median age was 45 years (range 7-76.9 years). The characteristics of the patients are listed in table I. Of the 144 patients with a documented ethnic background, 104 (71.2%) were Caucasians. HIV coinfection was present in 57/159 (36%) patients screened. Eighty-two patients (42.3%) were HBeAg-positive and 52 (26.8%) were currently receiving anti-HBV treatment (interferon: 9 patients, pegylated interferon: 3, lamivudine: 31, adefovir: 2, lamivudine and tenofovir: 7).
Seven HBV genotypes were found in the studied population. Genotypes A and D were the most common. Genotypes G and F were present in only 2.6% of the study population (table II).

No association was found between median age and HBV genotypes (P=0.28). There was a strong association between ethnicity and HBV genotypes (P<0.001 for the overall comparison). Genotype A was almost exclusively carried by Caucasian patients (94%), Africans were most frequent among genotype E (82%), and Asians were most prevalent among genotypes B and C (table I).

Factors relating to HBV genotypes A or D

Factors that may be associated with the most prevalent HBV genotypes present in our patient population (genotypes A and D), including sex, age (< 0 yrs vs >40 yrs), ethnicity, presumed mode of infection, PC and CP variant, HIV status, liver activity (A0-A1 vs A2-A3) and fibrosis (F0-F1 vs F2-F4) were analyzed by multiple logistic regression analysis. According to univariate analysis, 6 factors were significantly associated with HBV genotype A (P<0.1): age >40 years, sexual transmission of HBV, contamination via intravenous drug use, non asian ethnicity, presence of PC variant. These variables were introduced in a multivariable logistic model to test the independent factors associated with genotype A. Univariate analysis selected 3 factors associated with genotype D (P<0.1): intravenous drug use, non asain ethnicity, presence of PC variant. These variables were introduced in a multivariable logistic model to test the independent factors associated with genotype D.

Discussion

In view of the distinct geographic distribution of HBV genotypes, it is important to survey their epidemiology in a given country or region, since HBV genotypes may have some influence on the course of liver disease. The seven major HBV genotypes (A-G) were represented in a sample recruited in one major French region outside of Paris. This distribution may reflect local differences caused by various ethnicities of inhabitants and their individual lifestyles that may also differ all over France. In our opinion, our study is the first to systematically investigate patients with chronic hepatitis B (CHB) providing HBV DNA positivity. In addition, it is one of the first attempts to
HBV genotypes in Southwestern France

Investigate genotypes in mono-infected or HIV co-infected patients. Therefore, the findings of the present survey are likely to be representative of the CHB patient population in Southwestern France.

Our results showed a predominance of genotypes A and D in agreement with other investigators [15, 21].

Our results showed a predominance of genotypes A and D in agreement with other investigators [15, 21]. As evidenced by previous studies concerning the geographic distribution of HBV, genotypes A and D were predominantly found in Caucasians.

Table II. – Demographic, clinical, and virological characteristics of the 194 patients with reference to HBV genotypes.

<table>
<thead>
<tr>
<th>Features</th>
<th>Number (%)</th>
<th>Median Age (years-range)</th>
<th>Ethnicity (N=146)</th>
<th>Source of infection</th>
<th>HIV status (N=159)</th>
<th>Liver histology</th>
<th>HBcAg-positive (%)</th>
<th>Pre-C (N=188)</th>
<th>Mutant (%)</th>
<th>Core promoter (N=186)</th>
<th>Mutant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
<td>F</td>
<td>G</td>
<td>N</td>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Number (%)</td>
<td>99 (51)</td>
<td>13 (6.7)</td>
<td>11 (5.7)</td>
<td>31 (26.3)</td>
<td>15 (7.7)</td>
<td>1 (0.5)</td>
<td>4 (2.1)</td>
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<td>Median Age (years-range)</td>
<td>46 (22-75)</td>
<td>38 (10-63)</td>
<td>49 (24-65)</td>
<td>43 (7-77)</td>
<td>37 (30-67)</td>
<td>58</td>
<td>37 (35-40)</td>
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<td>Ethnicity (N=146)</td>
<td>N=74</td>
<td>N=11</td>
<td>N=10</td>
<td>N=36</td>
<td>N=11</td>
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<tr>
<td>Caucasian (%)</td>
<td>71 (96)</td>
<td>1 (9)</td>
<td>2 (20)</td>
<td>24 (67)</td>
<td>2 (18)</td>
<td>1 (100)</td>
<td>3 (100)</td>
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<td>African (%)</td>
<td>3 (4)</td>
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<td>10 (28)</td>
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<td>Asian (%)</td>
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<td>9 (62)</td>
<td>8 (60)</td>
<td>2 (5)</td>
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<td>Source of infection</td>
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<td>Sexual</td>
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<td>1 (1)</td>
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<td>1 (25)</td>
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<td>Drug Use</td>
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<td>Transfusion</td>
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<td>Vertical</td>
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<td>Iatrogenic</td>
<td>7 (7)</td>
<td>3 (23)</td>
<td>0</td>
<td>3 (6)</td>
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<tr>
<td>Unknown</td>
<td>48 (49)</td>
<td>9 (69)</td>
<td>10 (99)</td>
<td>30 (59)</td>
<td>13 (87)</td>
<td>1 (100)</td>
<td>2 (50)</td>
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<tr>
<td>HIV positive (%)</td>
<td>39 (45.3)</td>
<td>0</td>
<td>0</td>
<td>13 (24.2)</td>
<td>2 (20)</td>
<td>0</td>
<td>3 (100)</td>
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<td>Liver histology</td>
<td>N=43</td>
<td>N=6</td>
<td>N=6</td>
<td>N=20</td>
<td>N=5</td>
<td>N=0</td>
<td>N=1</td>
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<tr>
<td>Activity ≥2 (%)</td>
<td>33 (77%)</td>
<td>2 (33%)</td>
<td>4 (67%)</td>
<td>17 (83%)</td>
<td>3 (60%)</td>
<td>0</td>
<td>1 (100%)</td>
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<tr>
<td>Fibrosis &gt;2 (%)</td>
<td>27 (63%)</td>
<td>1 (17%)</td>
<td>2 (33%)</td>
<td>4 (20%)</td>
<td>3 (60%)</td>
<td>0</td>
<td>1 (100%)</td>
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<tr>
<td>HBcAg-positive (%)</td>
<td>52 (53)</td>
<td>3 (23)</td>
<td>6 (55)</td>
<td>18 (35.3)</td>
<td>2 (13)</td>
<td>0</td>
<td>2 (50)</td>
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<td></td>
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<tr>
<td>Pre-C (N=188)</td>
<td>N=96</td>
<td>N=13</td>
<td>N=10</td>
<td>N=51</td>
<td>N=15</td>
<td>N=1</td>
<td>N=3</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mutant (%)</td>
<td>7 (7.3)</td>
<td>8 (61.5)</td>
<td>6 (60)</td>
<td>28 (54.9)</td>
<td>13 (66.7)</td>
<td>0</td>
<td>3 (100)</td>
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<tr>
<td>Core promoter (N=186)</td>
<td>N=96</td>
<td>N=13</td>
<td>N=9</td>
<td>N=51</td>
<td>N=15</td>
<td>N=1</td>
<td>N=2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant (%)</td>
<td>45 (46.9)</td>
<td>2 (15.4)</td>
<td>7 (77.8)</td>
<td>18 (35.3)</td>
<td>7 (46.7)</td>
<td>0</td>
<td>1 (50)</td>
<td></td>
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</table>

HBV: human immunodeficiency virus; HBcAg: hepatitis B e antigen; pre-C: hepatitis C pre-core region.

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HBV is hyperendemic and genotypes B and C prevail. Of particular note was the detection of genotype G in four of the 194 (2.1%) patients in Southwestern France. Because genotype G was discovered in 2000 [7], epidemiological data are limited. HBV genotype G has been reported in France, Georgia, Germany, and Mexico, but not in Japan [7, 26-28].

We found a strong correlation between HBV genotypes and the presumed mode of infection, but the latter may merely be a surrogate marker of ethnicity or place of birth. However, multivariate analysis suggested rather the opposite since contamination via intravenous drug use and non-Asian ethnicity were independently associated with genotype A. Genotype A was prevalent among patients infected via sexual route, genotype D was related to all modes of infection, and genotypes B and C were exclusively present among patients with vertical transmission or other routes of infection. Another important finding of our study was the strong association between HIV status and HBV genotypes. HIV infection was common in patients with genotypes A and D and absent in patients with genotypes B and C.

The majority of studies on the effect of genotypes on disease progression have been undertaken in South-east Asia where HBV is hyperendemic and genotypes B and C prevail. These studies showed that genotype C was associated with higher virus loads [29] and more aggressive liver disease [17, 30]. On the other hand there is a dearth of studies comparing genotypes A and D. In India, genotype D is reported to be associated with more severe liver disease than that associated with genotype A. In contrast, in our study, genotype A was associated with METAVIR fibrosis score F2-F4 in univariate analysis. This result was not confirmed in multivariate analysis. Maybe it is linked to the high prevalence of HIV seropositivity in this group (many studies having shown HIV coinfection as a factor in HBV disease progression), or to the high proportion of patients over 40 yrs. However we cannot exclude a protective specific evolution linked to genotype A.

In keeping with the results from other investigators, genotype A and C were associated with a higher prevalence of HBsAg compared with genotypes B and D [12, 31-33]. Several studies reported a correlation between HBV genotype and HBeAg clearance. These studies found that the prevalence of HBeAg was higher in patients with genotype B compared to those with genotype C suggesting that HBeAg clearance occurred at higher rates among patients with genotype B [13, 16]. Unfortunately, the cross-sectional design of our survey could not address the issue of the association of HBV genotypes with HBeAg seroconversion that has been recently suggested [14, 16]. In multivariate analysis, HBeAg positivity was not an independent factor associated with genotype A. The PC/CP status could probably explain the difference between genotypes A and D concerning HBeAg positivity or negativity more than HBeAg clearance.

Our results clearly show in agreement with others [34] that HBeAg-negative chronic hepatitis is now the predominant form of chronic hepatitis B. In our population the overall proportion of HBeAg-negative chronic hepatitis B was 58%, lower than in a recent study [34]. This difference could be explained by a higher proportion of genotype A in our population, since genotype A is associated with a higher prevalence of HBeAg. Unfortunately, HBV genotyping was not performed by Zarski et al. We found that PC and CP variants were detected in a substantial proportion (35% and 43%, respectively) of our patients. In patients with chronic HBV infection, HBeAg negative disease is becoming the predominant form of infection and has therapeutic implications [35, 36]. This form of chronic HBV infection is highly prevalent in the Mediterranean (30-80%) and Eastern Asian

---

Table III – Independent factors associated with genotypes A or D in multivariate analysis.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;60 yr</td>
<td>3.97</td>
<td>1.71-9.21</td>
<td>0.001</td>
</tr>
<tr>
<td>HIV positivity</td>
<td>3.48</td>
<td>1.05-12.82</td>
<td>0.03</td>
</tr>
<tr>
<td>Absence of PC mutant</td>
<td>19.23</td>
<td>7.25-50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genotype D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Asian ethnicity</td>
<td>27</td>
<td>1.63-53</td>
<td>0.04</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>6.17</td>
<td>1.33-24.48</td>
<td>0.009</td>
</tr>
<tr>
<td>PC mutant</td>
<td>4.12</td>
<td>1.64-10.35</td>
<td>0.002</td>
</tr>
</tbody>
</table>

HIV: human immunodeficiency virus; PC mutant: pre-core mutant.
detected in HBeAg-negative patients, whereas CP variants were
but its basis has not been deciphered.
PC (G1896A) variant is related to base pairing in the stem-loop
HBV genotype B. The association between HBV genotypes and
among HBV genotypes A, C, D and E and relatively rare among
survey, CP variants (A1762T, G1764A) were evenly distributed
HBeAg-positive chronic hepatitis [37].

Our study showed that PC variants were predominantly
detected in HBeAg-negative patients, whereas CP variants were
found in both HBeAg-negative and HBeAg-positive patients, as
described by others [40, 41]. A more marked increase in the
prevalence of PC versus CP variants in HBeAg-negative patients is
attributed to the fact that PC (G1896A) variants abolish
down-regulate HBeAg production.

This study has identified three independent factors associated
with genotype A in HBV infected patients: age >40 yrs, HIV posi-
tive status, and absence of PC variant. The proportion of patients
with age >40 yrs was significantly higher, a finding consistent
with the recent results of a survey performed in France by
Ganne-Carrié et al. [22] in which the mean age of patients
infected by HBV genotypes B, C, and E was significantly lower
than HBV/A and JD. In keeping with the results from three
recent studies [42-44] in which 57%, 92%, and 70% of HIV-
infected patients were infected by HBV genotype A, this geno-
type was strongly associated with HBV infection in our study.

In summary, seven HBV genotypes were present, and PC and
CP variants could be detected in approximately one-third of
patients with genotype D and rare in patients with genotype A. In our
study, CP variants (A1762T, G1764A) only down-regulate
HBeAg production.

REFERENCES
2. Wright TL, Lau JYN. Clinical aspects of hepatitis B virus infection.
3. Orton E, Mizukami M, Inu Y, Moriyama EN, Kameoshima N,
Yamasato M, et al. Host-independent evolution and a genetic classi-
fication of the hepadnavirus family on based nucleotide sequences.
4. Okamoto H, Tsuda F, Sakugawa H, Maltezou HC, Gane-Carrié N,
Koda K, et al. Typing hepatitis B virus by homology in nucleo-
tide sequence: comparison of surface antigen subtypes. J Gen Virol
Comparison of the amino acid sequences of nine different serotypes of he-
padnavirus surface antigen and genomic classification of the corre-
6. Norder H, Courouce AM, Magnius L. Complete genomes, phylogene-
tic relationships, and structural proteins of six strains of the hepatitis B
virus, four of which represent two new genotypes. Virology 1994;
198:485-503.
7. Steyerer L, De Gendt S, Van Geyt C, Zoulim F, Fried M, Schinaier RP,
et al. A new genotype of hepatitis B virus: complete genome and phy-
8. Norder H, Hammer B, Lee SD, Bilek K, Courouce AM, Madsenheir IK,
et al. Genetic relativeness of hepatitis B viral strains of diverse geogra-
physial origin and natural variations in the primary structure of the
9. Bowyer SM, van Staden L, Kew MC, Sim JG. A unique segment of the
hepatitis B virus group A genotype identified in isolates from South Af-
racterization of hepatitis B virus genotypes among Yuipa Indians in
11. Lok AS, Akaka U, Greene S. Mutations in the pre-core region of
hepatitis B virus serve to enhance the stability of the secondary struc-
ture of the pre-genome encapsidation signal. Proc Natl Acad Sci USA
et al. Hepatitis B virus infection: precore mutations and its relation to vi-
et al. A case-control study for clinical and molecular biologi-
cal differences between hepatitis B viruses of genotypes B and C.
14. Chu CJ, Hassan M, Lok AS. Hepatitis B virus genotype B is associ-
ated with earlier HBeAg seroconversion compared with hepatitis B vi-
15. Sanchez-Tapia JM, Corta J, Mao A, Brusigero M, Rodés J. Influence
of hepatitis B virus genotype on the long-term outcome of chronic hepa-
16. Lindh M, Hansson C, Dilllon AP, Norkean G, Horal P. Core promo-
ter mutations and genotypes in relation to viral replication and liver
damage in East Asian hepatitis B virus carriers. J Infect Dis 1999;179:
753-62.
17. Kao JH, Chen PI, Lai MY, Chen DS. Hepatitis B virus genotype corre-
culate with clinical outcomes in patients with chronic hepatitis B. Gastro-
998-1002.
19. Wai CT, Chu CJ, Hassan M, Lok AS. HBV genotype B is associated
with better response to interferon therapy in HBeAg (+) chronic hep-
Cakaloglu Y, et al. Pegylated interferon alfa-2b alone or in combina-
tion with lamivudine for HBeAg-positive chronic hepatitis B: a ran-
Multicenter study of hepatitis B virus (HBV) genotypes in France:
correlation with liver fibrosis and hepatitis B e antigen status. J Viral
22. Game-Carrié N, Williams V, Kadish H, Tranchet JC, Dotti-Mendi S,
Allou C, et al. Significance of hepatitis B virus genotypes A to E in a
cohort of patients with chronic hepatitis B in the South Saint Denis dis-
23. Binquet C, Clémeur V, Gagnon-Gildard H, Jouvent V, Serves M,
Lacoste D, et al. Modeling changes in CD4-positive T-lymphocytes
counts after the start of antiretroviral therapy and the relation with risk of opportunistic infections: the Aquitaine Cohort, 1996-1997. Am
Epidemol 2001;153:386-93.
24. Brunkhorst Y, Fleury H, Timsitode P, Pellegrin I, Uribelarrui R,
Katlama C, et al. Anti-hepatitis B virus efficacy of tenofovir disoproxil
25. Cho SW, Hahn KB, Kim JH. Reversion from precore/core promoter
mutations to wild-type hepatitis B virus during the course of lamivudine
mination of hepatitis B virus genotype G by polymerase chain reac-
27. Sanchez LV, Maldonado M, Bastidas-Ramirez BE, Norder H, Caroli M,
Panduro A. Genotypes and S-gene variability of Mexican hepatitis B
virus, four of which represent two new genotypes. Virology 1994;
199:4077-81.
28. Vieth S, Manegold C, Drosten C, Nippraschk T, Gunther S. Sequence
and phylogenetic analysis of hepatitis B virus genotype G isolated in


