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Prevalence of HBV Genotypes in Central and Eastern Europe

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The importance of hepatitis B virus (HBV) genotypes for disease progression and response to interferon-alpha-based treatment is well established. While almost all patients in the Mediterranean area are infected with HBV genotype D, HBV genotype A is dominant in Northern Europe. However, the distribution of HBV genotypes is unknown for several Central and Eastern European countries. Data are described of 1313 HBsAg-positive patients recruited at 14 referral centers in eight countries. There were only very few cases of HBV genotype B, C, E, F, and H infection while HBV genotypes A and D were found in 42% and 48% of patients, respectively. Eight percent of patients had positive bands for more than one genotype using the hybridization assay. The frequency of genotype A was higher in Poland (77%) and the Czech Republic (67%) as compared to Hungary (47%), Lithuania (41%), Croatia (8%), and Germany (32%). In contrast, HBV genotype D was most frequent in Croatian, Romanian, and Russian patients with 80%, 67%, and 93% of cases, respectively. In conclusion, HBV genotype A versus D showed significantly different distribution patterns in Central and Eastern Europe which deserves consideration for national guidelines and treatment decisions. ***J. Med. Virol. 80:1707–1711, 2008.*** © 2008 Wiley-Liss, Inc.

KEY WORDS: HBV genotype; hepatitis B

INTRODUCTION

The hepatitis B virus (HBV) shows significant sequence divergence. Subsequently, eight genotypes have been described [Fung and Lok, 2004; Norder et al., 2004]. The natural history of chronic hepatitis B differs between HBV genotypes with progression of fibrosis

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[Sanchez-Tapias et al., 2002; Buti, 2003; Chu et al., 2003; Kao and Chen, 2005] and the development of hepatocellular carcinoma [Orito and Mizokami, 2003; Chen et al., 2006] can vary among genotypes. In addition, response to interferon-alpha-based treatment has been shown to be greater in patients infected with HBV genotype A than in patients infected with genotype D [Erhardt et al., 2005; Wiegand et al., 2007]. This finding has been confirmed recently in treatment trials using pegylated interferons both for HBeAg-positive [Janssen et al., 2005; Lau et al., 2005] and HBeAg-negative patients [Bonino et al., 2007]. In contrast, the response to treatment with nucleoside or nucleotide analogues is rather independent from HBV genotypes [Westland et al., 2003; Lurie et al., 2005; Wiegand et al., 2007]. Subsequently, HBV genotype analysis was recommended in the German Guidelines for the management of patients with hepatitis B [Cornberg et al., 2007].

The worldwide distribution of HBV genotypes shows significant differences. While in Asia most patients are infected with genotypes B or C [Liu et al., 2005], persons living in the Mediterranean Area carry mainly the HBV genotype D. In contrast, genotype A is more frequent in Northern Europe. Limited data on HBV genotype distribution are available for most Central and Eastern European countries. Previous studies from Poland and from the Czech Republic have described a dominance of HBV genotype A [Bielawski et al., 2004; Nemecek and Strunecky, 2004; Zalewska et al., 2005; Slusarczyk et al., 2006], while no data are available for countries such as Romania or the Baltic states. However, information on HBV genotypes has increasing importance considering that the migrational behavior of the European population is changing with more states becoming members of the European Union. In Western and Northern European countries HBV infection is mainly a disease of immigrants [Gjorup et al., 2003; Hahne et al., 2004; Marschall et al., 2005]. For example, 30–54% of HBsAg-positive patients in Germany were born either outside Europe, in countries belonging to the former Soviet Union, in Eastern Europe, or in the Mediterranean area [Erhardt et al., 2005; Niederau et al., 2007]. Thus, the aim of this study was to investigate the distribution of HBV genotypes in HBsAg-positive persons recruited in eight Central and Eastern European countries.

METHODS

Fourteen major national referral centers in eight Central and Eastern European countries took part in this study. A central data base was set up in Hannover within the European Network on Viral Resistance VIRGIL. Each site reported data on HBV genotypes in an anonymous form. In addition, HBV viral load, biochemistry, hematology and liver histology were recorded, if available. Overall, 1313 patients were included from Romania, Hungary, the Czech Republic, Germany, Poland, Lithuania, Russia, and Croatia (Table I). Selection of patients for this study was based on the availability of data on HBV genotypes only. The participating sites were asked to report all patients with the available respective information. Three sites performed prospectively HBV genotyping for this study while 11 sites reported pre-existing data on file. Possible selection bias includes HBV-DNA levels and the clinical indication to determine the HBV genotype. Thus, HBsAg carriers without quantifiable HBV-DNA could not be included since it is not possible to determine the HBV genotype in these patients. On the other hand, patients who have been candidates for interferon alpha-based treatment might have been over-represented in this cohort.

HBV genotypes were determined by the Inno-LIPA hybridization assay in 79% of cases according to the manufacture's instruction (Inngenetics, Gent, Belgium). The performance of this assay has been described in detail before [Qutub et al., 2006]. In the remaining 21% of patients, HBV genotypes were determined by HBV-DNA amplification and subsequent sequencing of the HBV surface gene according to the established protocols in the respective centers.

HBV-DNA was isolated from serum samples using the QiaAmp blood kit (Qiagen, Hilden, Germany) and subjected to PCR. The primers and reaction conditions used for PCR amplification were chosen from the HBV surface gene (HBs-gen) as described previously [Toan et al., 2006]. PCR fragments were analyzed by direct DNA sequencing on both strands using primers as described previously [Song et al., 2003]. The sequences obtained were matched with the National Centre for Biotechnology Information GenBank and compared with recently described HBV-prototypes (Accession No. for: HBV-A Z72478; HBV-B D00329; HBV-C

TABLE I. Prevalence of HBV Genotypes in Central and Eastern Europe

	Genotype A	Genotype B	Genotype C	Genotype D	Genotype E	Genotype F	Genotype G	Genotype H	Mixed Genotypes
Overall, n = 1313	545 (42%)	11 (0.9%)	15 (1.2%)	628 (48%)	1 (0.1%)	3 (0.3%)		5 (0.4%)	105 (8%)
Romania, n = 245	15 (6%)			164 (67%)					66 (27%)
Hungary, n = 255	119 (47%)	3 (1.2%)	4 (1.6%)	110 (43%)					19 (7.4%)
Czech Republic, n = 209	140 (67%)	6 (2.9%)	4 (1.9%)	59 (28%)					
Germany, n = 133	43 (32%)	2 (1.5%)	7 (5.3%)	78 (58%)	1 (0.8%)	1 (0.8%)			1 (0.8%)
Poland, n = 248	190 (77%)			47 (19%)		2 (0.8%)		5 (2.0%)	4 (1.6%)
Lithuania, n = 63	26 (41%)			34 (54%)					3 (4.8%)
Russia, n = 60	4 (6.7%)			56 (93%)					
Croatia, n = 100	8 (8%)			80 (80%)					12 (12%)

X01587; HBV-D V01460; HBV-E X75657; HBV-F X75658; HBV-G AF160501).

RESULTS

Data on HBV genotypes are described for 1313 HBsAg-positive patients recruited in eight Central and Eastern European Countries (Romania n = 245, Croatia n = 100, Hungary n = 255, Czech Republic n = 209, Germany n = 128, Poland n = 248, Lithuania n = 63, Russia n = 60).

Overall, genotype D and A were detected in 628 (48%) and 545 (42%) patients, respectively. While these findings were expected, significant differences in HBV genotype distribution between individual countries were noted. While genotype A was dominant in Poland (77% of cases) as reported previously [Bielawski et al., 2004; Slusarczyk et al., 2006], also patients from the Czech Republic were infected in 67% of cases with HBV genotype A. In contrast, genotype D was detected more frequently than genotype A in Russia (93%), Croatia (80%), Romania (67%), Germany (59%), and Lithuania (54%). Hungary showed an intermediate distribution with an almost equal distribution of HBV genotypes A and D (Table I).

As expected for a Central and Eastern European population with a low frequency of immigrants from Asia, Africa and Central and South America, there were only very few patients with HBV genotype B (0.9%), C (1.2%), E (0.1%), F (0.3%), and H (0.4%) infection. The 26 patients with HBV genotype B or C were all reported from Hungary, the Czech Republic, or Germany. For 11 patients it was confirmed that the respective genotype B and C patients were indeed born in Asia. For the other 15 patients the country of birth was not reported.

Another interesting finding was that 105 patients (8%) of this European hepatitis B cohort showed evidence of mixed genotype infection. This was evident particularly in Romanian patients where in 27% of cases the hybridization assay showed reactivity's to more than one genotype. In most cases (82%) bands specific for genotype A and D were positive. However, 11 cases also showed other patterns with A/D/F, D/E/G, D/F/G, and D/G being the most frequent. It is not known whether the patients were indeed infected with more than one genotype or whether viruses with intergenotype recombinations were present as described previously [Simmonds and Midgley, 2005].

The clinical presentation of HBV genotype D and genotype A infection was slightly different (Table II), as expected from previous studies [Sanchez-Tapias et al., 2002]. Genotype A patients were older than genotype D patients (43 years vs. 38 years; $P < 0.001$), Genotype A patients were HBeAg positive (54% vs. 36%; $P < 0.001$) more frequently. This can be explained in part by the fact that precore mutants do not occur in genotype A [Li et al., 1993; Bonino et al., 2007].

DISCUSSION

This study on HBV genotype distribution in Eastern Europe showed a clear geographical shift with HBV genotype D being dominant in South-East Europe (Romania and Croatia) and Russia in contrast to genotype A being most frequent in the more "Western" countries Poland and the Czech Republic. About one-third of German patients infected with HBV are of Turkish origin although no information on the country of birth was available for this study. A recent study from Düsseldorf which is located in western Germany with even higher proportions of immigrants from the Mediterranean area has reported genotype D infection in 40% of patients [Erhardt et al., 2005]. In contrast, other central European countries such as Poland and the Czech Republic are still quite uniform ethnically, for example, the proportion of immigrants does not exceed 3–4% [Bielawski and Stalke, 2005].

These data indicate that the emerging epidemiology of HBV infection in Central and Eastern Europe is not due to immigration of HBsAg-positive persons from high endemic Asian countries. HBV genotypes E and F were found in four patients only (two German and two Polish persons) which is rather low compared to other previous reports from western and southern European countries. Previous reports on genotypes E and F infection in Europe came mainly from France, Spain, and Italy, which reported higher prevalence of genotypes E and F than it was observed in this study [Sanchez-Tapias et al., 2002; Ganne-Carrie et al., 2006; Medici et al., 2006].

Another interesting finding was the rather high frequency of mixed genotypes in South-Eastern Europe. The A/D pattern was evident in particular in Romania. It is tempting to speculate that gypsies traveling in Eastern and Central Europe during the last centuries may have been exposed to different viruses and thereby have carried diverse viruses to Romania. Unfortunately, in this study it was not possible to investigate these

TABLE II. Clinical Presentation of HBV Genotype A and Genotype D Infection

	Genotype A	Genotype D	*P*-value
HBeAg negative (%), n = 580	46%	64%	<0.001
HBV-DNA (median log 10 IU/ml), n = 762	8.4	7.4	0.07
ALT (mean ± SD IU/ml), n = 345	111 ± 124	75 ± 95	<0.001
AST (mean ± SD IU/ml), n = 271	89 ± 90	58 ± 80	0.003
Platelets (mean ± SD 10^3/μl), n = 188	186 ± 77	207 ± 53	0.07

patients in more detail as no serum was stored to perform cloning and sequencing experiments. More detailed data on the clinical course of patients with mixed infection was also not available. Direct sequencing and the Inno-LIPA hybridization assay have different sensitivities and thus do detect mixed genotypes in a different percentage. It well maybe that mixed genotypes were underreported by centers using direct sequencing. However, the hybridization assays were used by most sites and 79% of patients were tested with this method. Future studies are needed to address the role of mixed genotype infection in Romanian patients in greater detail.

The percentage of genotype A in HBeAg negative patients was surprisingly high in our cohort. It is likely that many of the HBeAg-negative patients were HBeAg-positive patients who had already experienced spontaneous HBe-seroconversion without having selected the precore stop-codon variant. A trend toward higher HBV-DNA was documented for patients with HBV genotype A presumably due to more HBeAg positive patients in this group. Biochemical activity as determined by ALT and AST levels were significantly higher in genotype A. However, data on liver histology were only available for a minority of patients precluding further meaningful statistical analysis.

This study has several limitations. First, a selection bias cannot be excluded for all centers as HBV genotyping may have been performed preferentially in patients considered for interferon therapy. However, in most centers a randomly selected group of patients was selected for HBV genotyping and thus the reported prevalence of the respective genotypes should be representative. Another bias could be that genotyping was not possible in patients with HBV-DNA which could not be quantified and that the prevalence of HBV genotypes could have been different in low viremic HBeAg-negative patients, the so called HBsAg carriers. The high proportion of genotype A in patients without HBeAg suggests that a significant number of patients were low viremic carriers. Moreover, clinical data were available only for a subgroup of patients as participating sites were frequently diagnostic laboratories without full access to clinical information. For example, the exact number of co-infections with HCV cannot be given for all centers but it was below 10% in centers having this information. Also other clinical information was not complete and no monitoring of data was possible. Therefore, no further statistical analysis was undertaken.

In summary, this first comprehensive analysis of HBV genotype distribution in more than 1300 HBsAg-positive patients in Central and Eastern Europe showed significant differences in the frequency of genotype A versus D between countries while all other genotypes were rare. Furthermore, a significant proportion of European patients may carry mixed genotype infections or recombinant viruses. The surprisingly high prevalence of HBV genotype A in some countries needs to be considered for national guidelines and treatment decisions.

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