

Original article

Distribution of HBV genotypes in Poland

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Abstract

Aim of the study: To identify distribution of HBV genotypes in particular regions of Poland.

Material and methods: The study included 270 treatment-naïve, HBV-infected individuals, enrolled in 7 centers of Poland. HBV genotyping was performed in 243 of them with the INNO-LiPA HBV Genotyping assay (Inno-genetics).

Results: Genotype A present in 2/3 patients was demonstrated as the most predominant in Poland. It was followed by D (20%), H (5%) and mixed A + D (5%). Remaining patients were infected with genotype F, mixed D + G, A + C or D + F. Analysis of distribution demonstrated regional differences, with a higher rate of genotype D prevalence (about 30%) in the eastern (Białystok and Lublin) and south-western (Wrocław) parts compared to other regions, where the prevalence rate was below 15%. The highest prevalence of genotype A (exceeding 80%) was observed in central Poland (Bydgoszcz, Łódź).

Conclusions: The presented data reveal the current distribution of HBV genotypes across Poland, which is the first and the largest such epidemiological analysis.

Key words: HBV, epidemiology, hepatitis, genotypes.

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Introduction

Infection with hepatitis B virus (HBV) remains a huge public health issue all over the world [1]. A third of the world population, which is approximately 2 billion people, reveals serologic infections with HBV in the past or currently [1]. It is estimated that approximately 1 million people per year die due to acute and chronic infections with HBV. A few viral factors exist which may influence infections with HBV including HBV DNA genotype and mutations in surface HBV (S), precore (PC) and basic core promoter (BCP) [2].

One feature of HBV is sequence heterogeneity of the virus caused by the lack of polymerase activity [1].

Analysis of HBV sequence divergence enables identification of 10 genotypes of HBV (A-J) and a few subgenotypes noted worldwide [3,4]. No subgenotypes for genotypes E and G have been described [5,6]. HBV genotypes are differently allocated geographically, which may indicate the way of HBV spreading. Genotype A (HBV-A) is common in Sub-Saharan Africa (subgenotype A1), Northern Europe (subgenotype A2), Western Africa (subgenotype A3) and in northern Italy (Table 1) [2,7,8]. Genotypes B and C are

Table 1. Characteristics of patients included in the study

Gender, M/F (%)	140/130 (52/48)
Age, median years (range)	35 (25-43)
HBeAg-positive, n (%)	14 (5)
ALT > ULN, n (%)	66 (24)
ALT, median IU/ml (IQR)	28 (20-40)
HBV DNA > 2000 IU/ml, n (%)	141 (52)
HBsAg, median IU/ml (IQR)	13 436 (3744-23 134)
Liver fibrosis, n/N > F1 (%)	33/184 (18)

ALT – alanine aminotransferase, ULN – upper limit of normal

common in Asia and in the Pacific region. However, the indicators of genotypes B and C occurrence differ between different Asian countries. HBV-C occurs more frequently than HBV-B in China, Japan and Korea and HBV-B is more frequent in Taiwan and Vietnam [2,7,8]. What is worth mentioning is the fact that almost every patient with chronic hepatitis B in Korea is infected with HBV-C. Genotype D is frequently seen in patients with HBV in Southern and Eastern Europe. According to WHO classification, genotype D is the most common in Iran [3,7,9].

Infections with other genotypes are rare, but their epidemiology has been characterized widely [7,9]. Genotypes E and F were discovered in Western Africa, Southern USA, Central and Southern America as well as Central Europe [5]. HBV genotype E occurs in Western Africa. Genotype F is commonly seen in Central and Southern America, especially in Buenos Aires, Argentina [10]. The case of Rosario city seems to be interesting due to the fact that although it is located 150 miles north of Buenos Aires, the most common genotype there is A, which is probably connected with the large number of Italian immigrants [11]. Genotype G has been observed in France, Germany and United States. Genotype H is seen in Central America. Two additional genotypes have been identified recently: genotype I in Laos and Vietnam and genotype J in Ryukyu Island, Japan [3,4,9]. Up to now, studies which evaluated HBV genotypes in Poland were carried out about 10 years ago, based on the data from one center, and included a relatively small number of patients [12,13]. There has been no study that involved a sufficient number of patients to perform analysis on genotypes' regional distribution.

The EpiGeneS study was designed for a long-term cohort analysis of an effect of baseline host and viral factors associated with chronic HBV infection on disease progression and treatment efficacy.

The aim of the EpiGeneS study at this stage was to identify prevalence of particular HBV genotypes

and possible regional distribution differences in Poland, as the baseline characteristics of the studied population.

Material and methods

In this multicenter, cross-sectional study, 270 treatment-naïve individuals with persistent HBV infection were initially enrolled in 7 university centers in Poland (2013-2014). Inclusion criteria were not restricted by hepatitis B e antigen (HBeAg) status, alanine aminotransferase (ALT) activity or HBV-DNA. However, viral load should be on the level allowing for genotype quantification. Exclusion criteria were: hepatitis C (HCV), human immunodeficiency (HIV) and hepatitis D (HDV) viral co-infections, previous anti-HBV therapy, autoimmune disorders, neoplastic disorders and immunotherapy. HBV genotyping was performed in 243 persons who demonstrated a sufficient HBV-DNA level with the INNO-LiPA HBV Genotyping assay (Innogenetics) by the central laboratory for all involved centers (Synevo). All participants signed informed consent and this study was approved by the Ethical Committee of the Medical University of Białystok. The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Results

As demonstrated in Table 1, the majority of patients included in the study were relatively young. The large majority of them were HBeAg-negative, and demonstrated normal ALT activity and a low stage of liver fibrosis. More than half showed HBV DNA exceeding 2000 IU/ml and all had hepatitis B s antigen (HBsAg) above 3700 IU/ml.

According to data in Table 2, the most predominant genotype in Poland is A, confirmed in 2/3 of patients included in the study. The second is D followed by genotype H and mixed A + D. The remaining 2% consisted of 1 patient with genotype F and mixed genotypes D + G (3 patients), A + C (1 patient) or D + F (1 patient). Altogether 92% of Polish patients were infected with genotype A or D. However, collected data demonstrated differences in genotype distribution between particular regions of the country, with a higher rate of genotype D prevalence (about 30%) in the eastern part (Białystok and Lublin) and south-western part (Wrocław) compared to other centers where the prevalence rate was below 15%. The highest prevalence rate of genotype A, exceeding 80%, was observed in central Poland (Bydgoszcz, Łódź).

Table 2. Prevalence of HBV genotypes in selected regions of Poland

	Białystok	Lublin	Łódź	Wrocław	Szczecin	Chorzów	Bydgoszcz	Poland
A	32 (48%)	12 (57%)	6 (86%)	17 (59%)	3 (75%)	23 (77%)	71 (83%)	164 (67%)
D	18 (27%)	7 (33%)	1 (14%)	8 (28%)	0	2 (7%)	12 (14%)	48 (20%)
H	7 (11%)	1 (5%)	0	1 (3%)	1 (25%)	1 (3%)	2 (2%)	13 (5%)
A + D	7 (11%)	0	0	2 (7%)	0	3 (10%)	0	12 (5%)
Other	2 (3%)	1 (5%)	0	1 (3%)	0	1 (3%)	1 (1%)	6 (2%)
	66	21	7	29	4	30	86	243

Discussion

In Poland, over 1500 HBV infections per year are diagnosed, and the number of infected patients is estimated to be between 400 and 600 thousand. The estimated number of HBV carriers (HBsAg-positive) is 1.3% of the population [14]. In reports published so far in Poland, genotypes A and D are predominant. Zalewska *et al.* [12] discovered genotype A in 78.8% of HBV carriers and in 13.6% it was genotype D. Slusarczyk *et al.* confirmed predominance of genotype A, which was discovered in 56 of 65 patients (86.1%). Genotype D was demonstrated in 6 (9.2%) and A + D in 3 (4.6%) [13]. The multicenter EpiGeneS study which started in 2013 included a large group of treatment-naïve patients, who will be followed for possible associations between treatment type, viral genotypes, HBsAg levels, course of the disease and other possible predictors of treatment efficacy. At the current stage 270 patients have been included and samples collected from the majority of them allowed analysis of HBV genotype distribution in Poland to be performed.

The study confirmed predominance of genotype A in all regions of Poland, with the highest rate in the central part of the country. Data from Bydgoszcz and Łódź demonstrating a rate exceeding 80% are in line with previous data from Warsaw [13]. In addition, we were able to show geographical differences in distribution of genotype D, which seems to be more frequently seen in patients from eastern (Białystok, Lublin) and south-western (Wrocław) than in other regions of Poland, which was never demonstrated in the past.

In 17 (7%) patients we were not able to demonstrate one genotype responsible for HBV infection, possibly suggesting damage of adaptive immunity in these cases, which will be interesting with respect to future follow-up of these patients and the possible effect of treatment [5].

The type of HBV genotype may significantly influence the risk of hepatocellular carcinoma (HCC) development and progression of the disease [5]. It was

demonstrated that genotypes A, B and D are associated with lower risk of hepatocellular carcinoma compared to genotype C [15,16], but patients infected with genotype C and D reveal higher risk of progression of the disease which may be related to worse clinical prognosis in comparison to patients with genotype A and B [1,7]. However, there are also reports of studies which did not demonstrate any association between HBV genotypes and risk of HCC [17]. Discrepancies between those results, especially derived from the same regions, are not clear [1]. Moreover, genotype C in comparison to genotype B is associated with a higher frequency of core promoter mutation and a lower rate of response to interferon alpha treatment [5]. A study conducted in Alaska which included 1536 patients, after 20 years of follow-up revealed higher risk of HCC in patients infected with genotypes C and F [18].

It was demonstrated in several studies that genotype A infected patients respond better to treatment with IFN- α than those infected with genotype D, which has significant implications for the choice of treatment in Poland. On the other hand, there are no clear data on the association between HBV genotype and treatment response to nucleos(t)ide analogues as well as risk of resistance [5,19-21]. Therefore long-term follow-up of patients included in an EpiGeneS cohort will be of value when they start different treatment options.

In conclusion, the presented data reveal the current distribution of HBV genotypes across Poland, which is the first and the largest such epidemiological analysis. The well-characterized population of treatment naïve patients expecting possible therapy can serve as an excellent cohort for the further analysis of an effect of HBV genotypes and some other baseline factors on natural history of HBV infection and treatment efficacy with different therapeutic options.

Disclosure

Authors report no conflict of interest.

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