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DISTRIBUTION OF HCV GENOTYPES IN POLAND

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ABSTRACT

Available data on prevalence of HCV genotypes in Poland are insufficient. The aim of the study was the analysis of distribution of HCV genotypes in Poland over the period of recent 10 years regarding the age of patients and the regions of the country.

MATERIAL AND METHODS. Analysis of HCV genotypes in Poland was carried out between 2003 and 2012, and included 14 651 patients from 22 centers where patients with chronic viral hepatitis C are diagnosed and treated. Genotypes were analyzed in age groups (<20 years of age, 20-40 years of age, >40 years of age) as well as in populations of HBV and HIV co-infections.

RESULTS. Genotype (G) 1 infection was demonstrated in 79.4%, G2 -0.1%, G3- 13.8%, G4- 4.9%, G6-0.09% and mixed infections in 1.6%. There was no infection with genotype 5. The highest prevalence of G1 was observed in the Łódzkie voivodship (89.2%) and the Śląskie voivodship (86.7%) while the lowest one in the Warmińsko-mazurskie (62.0%) and the Podlaskie voivodships (68.2%). Genotype 3 most commonly occurs in the Warmińsko-mazurskie (28.1%), and the Podlaskie voivodships (23.0%) and is least common in the Małopolskie (7.9%) and the Łódzkie voivodships (9.0%). Genotype 4 is more common in the Kujawsko-pomorskie (11.7%) and the Podlaskie voivodships (8.6%) and relatively less common in the Lubelskie (1.1%) and the Łódzkie voivodships (1.8%). Prevalence of G1 infection in 2003-2004 was 72% and increased up to 85.6% in 2011-2012, that was accompanied by decrease of G3 prevalence from 17% to 8% in this period. In HBV co-infected (n=83), G1 infection was demonstrated in 85.5%, G3 – in 7.2%, G4 -4.8%, and mixed genotypes in 6%. Among HIV co-infected (n=391), a much lower prevalence of G1 (33.0%) and a high of G3 (40.4%) as well as G4 (24.0%) were observed.

CONCLUSIONS. There is a geographic variability of HCV genotypes prevalence in Poland. Increase of HCV G1 infections and decrease of G3 and G4 were observed in the last 10 years. Genotypes G3 and G4 occur more often in HCV/HIV co-infected than in HCV mono-infected patients.

Key words:*: HCV, genotype, epidemiology, Poland*

INTRODUCTION

The hepatitis C virus (HCV) was identified in 1989 and was determined as one of the most frequent etiological factors responsible for chronic liver diseases (1, 2). The most dangerous complication of chronic HCV infection is progressive liver fibrosis, which can lead to liver cirrhosis and failure (3,4). It is favored by lack of infection symptoms leading to latent development of the disease (5). The latest surveillance study of a large population showed HCV infection in approximately 1.9% of the population of Poland (6). As about 80-85% of HCV infections become chronic form of the disease, a majority of patients will require antiviral therapy (7).

Significant differences between particular genotypes (G), reaching 30-35%, were determined while comparing the nucleotides sequence of HCV genome (8). The occurrence of particular HCV genotypes and subtypes is characterized by big geographical differentiation (9). Genotypes 1, 2, and 3 are widely distributed in the USA, Europe, Australia, and the Eastern Asia (China, Japan, and Taiwan), whereas HCV genotype 4 is predominant in the Middle East, Egypt, and the Central Africa and genotype 5 – in the Southern Africa and genotype 6 in the South-East Africa (9, 10).

The role of genotypes in the progression of the disease has not been explained yet (2). Many factors can affect pathogenetic differences in the course of the disease. The age of the infection is one of the factors, elderly show G1 infection with simultaneous and more frequent liver cirrhosis, liver insufficiency, and hepatocellular carcinoma (HCC), (11). Genotype 1b, more often than others, accompanies severe liver diseases, but on the other hand, faster progression of liver steatosis and fibrosis is observed in patients with G3 infection. Recent studies showed that infection with subgenotype 1b occurred significantly more often in patients with HCC (11). Current studies carried out in humans and chimpanzees did not show significant biological differences between particular HCV genotypes. All HCV genotypes as well as HCV subtypes are both hepatotropic and infective and lead to chronic infection. HCV genotype is a strong and independent prognostic factor of treatment effectiveness conditioning the type and duration of antiviral therapy. Those infected with G1 or G4 require longer and at the same time less effective therapy than G2- or G3-infected patients. It should be assumed that differences in the treatment of patients infected with various genotypes will grow together with new therapeutic possibilities in the future. Today a so called triple- therapy of standard pegylated interferon alpha (PegIFN-alpha) and ribavirin (RBV) with additional protease inhibitor (boceprevir or telaprevir) can be used only in case of genotype 1 infected and requires entirely different management (7).

It is important to know about the frequency of HCV genotypes occurrence in a population in order to establish pharmaceutical and financial prognosis of antiviral therapy. Currently available information concerning particular HCV genotypes occurrence in Poland are insufficient and come from small studies covering chosen populations or regions. Therefore, a national analysis of HCV genotypes occurrence in Poland seems to be of great importance.

MATERIAL AND METHODS

Data concerning particular HCV genotypes occurrence were obtained with the use of a questionnaire

filled by 22 Polish diagnostic centers where patients with hepatotropic viruses infections are diagnosed and treated. The questionnaire contained questions about the number of persons with a particular genotype (G1-G6) occurring in chronically HCV infected patients, diagnosed between 2003 and 2012, in the age groups: up to 20 years of age, 20-40 years of age, and above 40 years of age. There were also questions concerning the occurrence of particular HCV genotypes in patients co-infected with HIV or HBV. Due to lack of determination of subtypes 1a and 1b and 3a and 3b in some centers, only a partial analysis of their occurrence was performed. The questionnaire was conducted between April and November 2012.

RESULTS

Data of 14 651 patients with HCV infection and a determined virus genotype were analyzed. The analysis covered 13 voivodships and years 2003-2012. The most frequent was the infection with G1 which occurred in 79.4% of patients (Table I). The next as far as frequency was concerned were infections with G3 (13.8%) and G4 (4.9%). The occurrence of G2 and G6 was infrequent (0.1% and 0.09%, respectively). Mixed infection with two or more genotypes was demonstrated in 1.6% of HCV infected patients. There was no occurrence of G5 infection in Poland in this period of time. In the limited group of G1 infected patients (n=1411, data from 3 centers), predominance of subtype 1b was observed (97.5%). The highest percentage of G1 infections was demonstrated in the Łódzkie (89.2%), the Śląskie (86.7%) and the Wielkopolskie Voivodships (85%), whereas the lowest one – in the Warmińsko-mazurskie (62.0%) and the Podlaskie Voivodships (68.2%). The analysis of genotype 3 infections prevalence showed the highest level in the Warmińsko-mazurskie (28.1%) and the Podlaskie Voivodships (23.0%) while the lowest – in the Lubelskie (9.6%) and the Łódzkie Voivodships (9.0%).

G4 HCV infection is characterized by a relatively high variability in its occurrence in Poland. The highest percentage was observed in the Kujawsko-Pomorskie Voivodship with 11.7% of HCV infected population. On the other hand, particularly low percentage of G4 infected patients was shown in the Łódzkie (1.8%), the Śląskie (1%), and the Lubuskie Voivodships (1.1%).

Mixed infections were diagnosed mostly in the Mazowieckie (4.4- 9.7% of all HCV infections) and the Lubelskie Voivodships (5%).

The analysis of genotype occurrence in particular age groups (Table II) demonstrated predominance of G1 HCV infection in patients above 40 years of age (83.2%), while the lowest prevalence was observed in the group of 20-40-year-old patients (75.9%). The highest G3 occurrence was shown in 20-40-year-old patients (16.8%) and it was slightly lower after 40 years of age. However, it was assumed to be twofold lower in patients under 20 years of age when compared to those over 20. G4 HCV infection in children and adolescents under 20 is especially frequent and occurs in 11.4%, specifically in the Kujawsko-Pomorskie Voivodship. The risk of G4 infection decreases together with the age to 6.1% in 20-40-year patients and to 2.6% in patients over 40.

Table II. Prevalence of HCV genotypes according to age. of diagnosis

Genotype HCV	**<20 y**	**20- 40 y**	**>40 y**
G1, %	80,6	75,9	83,2
G2, %	0	0,1	0,1
G3, %	7,1	16,8	12,8
G4, %	11,4	6,1	2,8
G5, %	0	0	0
G6, %	0	0	0,1
Mieszane, %	0,8	1,0	0.9

Tabela I. Distribution of HCV genotypes in particular province of Poland (%)

Province (center)	Genotype HCV (G)						
	G1	G2	G3	G4	G5	G6	mixed
Warmińsko-Mazurskie (Giżycko), n=153	62,0	0	28,1	8,5	0	0	1,3
Podlaskie (Białystok), n=1040	68,2	0	23	8,6	0	0,1	0
Kujawsko-pomorskie (Bydgoszcz, Toruń), n=2550	75,2	0	12,8	11,7	0	0	0,2
Dolnośląskie (Wrocław), n=281	76,1	0,3	18,5	4,3	0	0,1	0,7
Mazowieckie (Warszawa) , n=2495	76,6	0,4	12,5	4,7	0	0,0	5,7
Pomorskie (Gdańsk), n=1110	79,1	0,3	13,8	5,2	0	0,6	0
Zachodniopomorskie (Szczecin), n=792	80,5	0	16,2	2,5	0	0	0,7
Świętokrzyskie (Kielce), n=1463	81,5	0	14,8	1,8	0	0	1,8
Lubelskie (Lublin), n=256	82,8	0	9,6	1,1	0	1,1	5
Wielkopolskie (Poznań), n=2578	85	0,1	10,5	3,1	0	0	1
Śląskie (Chorzów), n=279	86,7	0,3	11,8	1	0	0	0
Małopolskie (Kraków), n=277	89,2	0,7	7,9	2,2	0	0	0
Łódzkie (Łódź), n=1377	89,2	0	9,0	1,8	0	0	0
POLAND, n=14 651	79,4	0,1	13,8	4,9	0	0,09	1,6

Prevalence of G1 infections in Poland has been observed to increase over the period of recent 10 years (Table III). In 2003-2004, the frequency of G1 infections was 72% and increased to 85.6% in 2011-2012. A reverse tendency was observed regarding G3 infections. Ten years ago, the prevalence of G3 infections was 17.9% and it decreased to 8.4%. recently. In 2003-2004, the frequency of G4 infections was 9%. However, over the period of recent 8 years it remained on the same level of 4%. Mixed HCV infections were noted on the same level of 1-2% during last 10 years. The infection with G2 and G6 occurred without any significant frequency changes.

Table III. Prevalence of HCV genotypes in Poland between 2003 and 2012

	Genotype HCV						
	G1	G2	G3	G4	G5	G6	mixed
2003-2004, %	72,0	0	17,9	9,0	0	0	0,9
2005-2006, %	75,5	0	12,5	4,0	0	0	1,7
2007-2008, %	79,0	0,2	13,5	4,9	0	0,05	2
2009-2010, %	79,4	0,2	13,3	5,0	0	0	2,0
2011-2012, %	85,6	0	8,4	4,7	0	0,1	1,2

In population of identified 83 patients co-infected with HBV, G1 HCV infection was observed in 85.5%, G3 – in 7.2%, and G4 – in 4.8% (Table IV). In the group of 391 patients co-infected with HIV, G1 infection was observed only in 33%, G3 – 40.4%, and G4 – in 24% (Table V).

Table IV. Prevalence of HCV genotypes in patients co-infected with HBV and HIV (data of HCV/HIV obtained from 10 centers and HCV/HBV from 7 centers).

	Genotype HCV (G)						
	G1	G2	G3	G4	G5	G6	mixed
HBV, (%) n=83	85,5	0	7,2	4,8	0	0	6,0
HIV, (%) n=391,	33,0	0	40,4	24,0	0	0	2,8

DISCUSSION

The risk of HCV infection varies and depends on many, not yet defined, factors. There are big differences of HCV incidence in various parts of Europe (Table V). The knowledge concerning the problem is differentiated, which is caused by lack of uniform screening procedures and HCV surveillance programs. General data show that there is approximately 3% (170-190 million) of HCV infected population in the world, with about 3-4 million patients infected every year. In Poland, different rate of HCV infections was notified depending on the population examined. The lowest frequency of anti-HCV antibodies

Table V. Prevalence of HCV genotypes in chosen European countries, Israel, Turkey and Canada

	Genotype HCV (G)						
	G1	G2	G3	G4	G5	G6	mixed
England	45	10	40	5	X	X	X
Sweden	45,2	19,3	33,8	1,7	X	X	X
Grece	47	8,3	27	15,2	X	X	X
Switzerland	51	9	30	10	X	X	X
Portugal	52,2	2,4	34	7	X	X	X
France	57	9,3	20.8	8,9	2,7	0,2	0,9
Canada	60	15,4	22,3	X	X	X	X
Norway	61,5	10,5	28	X	X	X	X
Germany	61,7	6,9	28	3,2	0,2	X	
Italy	62	27	7	5	X	X	X
Espana	64,4	3,1	19,6	11,6	0,3	X	X
Israel	70	8	20	3	X	X	X
Czech Republic	79,3	1	19,7	X	X	X	X
POLAND *	**79,4**	**0,1**	**13,8**	**4,9**	**0**	**0,09**	**1,6**
Hungary	85,5	0,8	3,4	1,7	X	X	X
Romania	93,4-99,1	X	X	X	X	X	X
Turkey	97,1	0,9	1,4	0,6	X	X	X

*in case of Poland data presented in current study are provided
X – no data

occurrence was demonstrated in primary blood donors – 0.48%, with 18% of confirmed HCV-RNA in this group only (12). It seems that the predominant paths of HCV infections changed over last years. Up to 1989, post-transfusion infections were predominant, which are rare nowadays (13). The fixed source of HCV infection is still considered to be surgical and dental procedures, cosmetic procedures (tattoos), communication injuries, intravenous drug use, seldom sexual contacts (14, 15). German studies analyzing infection paths in 259 patients with acute HCV showed 28% to be iatrogenic infections (9). In Poland, about 70% of intravenous drug users are HCV infected, out of which a part is co-infected with HIV. In groups of high risk, mainly among HIV-infected patients, the risk does not decrease, only the paths of infection can change. Intravenous injections became less important and sexual path gives higher danger, particularly in MSM group.

The establishment of the proportion of particular genotypes among HCV patients is important in appropriate national health politics, e.g. in prognosis of infection effects, the evaluation of efficacy and cost of therapy in a given population, region or in case of introducing new therapeutic methods.

Genotype 1 predominates in HCV infections in Europe and the Northern America. In various parts of the world there is a big variability in HCV subtypes (Table V) (9). The presented data demonstrated the differentiation of HCV genotypes distribution in Poland. It is probably due to various paths of infection transmission or predominance of given genotypes in local societies. In Poland, genotype 1 is a predominant one and it occurs in 62-89.2% of HCV infected patients dependent

on the region. Similar occurrence of G1 HCV in Europe can be observed in the Czech Republic (79.3%) and in Hungary (85.5%). The occurrence of G1 subtypes was only partially analyzed due to insufficient data from questionnaires. However, it points to definite predominance of the subtype 1b. Among HIV-infected patients, only 33% revealed genotype 1. It undoubtedly results from determined infection paths and predominance of other HCV genotypes among intravenous drug users, still a dominant group among HIV infected. During the last 10 years, the increase in G1 HCV infections was noticed (from 72% in 2003-2004 to 85.6% in 2011-2012). Similar trends can be observed in other regions of Europe. G1 HCV infections are predominant in people over 40 (83.2%) while in the group of 20-40 years of age they present 75.9%.

Prevalence of G3 infections also vary in particular regions of the country from 7.9% to 28.1% of all HCV infections. The highest frequency of G3 infections occurred in the north-eastern Poland (the Podlaskie and Warmińsko-Mazurskie Voivodships). In European countries, G3 infection is characterized by high differentiation of occurrence from 3.5% in Hungary to 40% in England (9). As it was shown in data of patients with HIV co-infection, G3 is the most common genotype in this population (40.4%). In the period of recent 10 years, the frequency of genotype 3 infections in general population decreased from 17.9% (2003-2004) to 8.5%. It could be due to faster elimination of G3 infections from the environment, as a result of higher treatment efficacy rate. The analysis of G3 infections in the age groups showed a low prevalence among patients<20 years of age (7.1%) while the group of 20-40 showed 16.8% of HCV-infected patients. Since G3 infections dominate among HIV infected patients who underwent infection due to intravenous drug use and its more seldom among younger population, we can assume that decrease of G3 frequency may result from lower popularity of intravenous drugs and improved availability of disposable syringes and needles.

The occurrence of genotype 4 in Poland also depends on the region and varies from 1.0% to 11.7% of all HCV infections. In Europe, G4 occurs with the frequency of above 10% only in Spain, Greece, and Switzerland. On the other hand, Egypt showed nearly 90% of infected patients (9). Much higher prevalence of G4 (24%) was observed in HIV co-infected patients and in patients below 20 years of age (11.4%). The frequency of G4 infection decreases with age to 6.1% (20-40 years of age) and to 2.8% in above-40-patients. During the latest 8 years, the frequency of G4 infections prevailed at the similar level of 4-5%. There were few cases of G2 and G6 infections and there were no infection with G5 at all.

Fluctuations of HCV incidence during consecutive years and differentiation of occurrence dependent on territory and environment as well as professions could be observed in Poland (16, 17). Incidence rate noted in 2011 in the Silesian Voivodship was 2.92 (per 100 thousand inhabitants) while in the same period in the Lubelskie Voivodship it was 13,88 (18).

However, those coefficients did not reflect the actual condition as there was no uniform program of anti-HCV testing and there were differences in the way of collecting data and their reporting in consecutive years. There are also differences in incidences between rural and urban environments and between towns of different size, that probably are due to availability of health care. The difference between gender can also be seen and that also depends on the age (19). Annual HCV infections recorded up to 2004 did not exceed 2000 cases a year but in 2005-2006 a significant increase to 3000 cases was observed due to the change of reporting. However, during consecutive years, the number of recorded new incidences decreased (19). Data obtained from the Blood Regional Centers showed decreasing tendency in anti-HCV antibodies occurrence among primary and repeated donors, but it is not clear whether this trend is sustained (12, 20). It should be noticed that the awareness of the society concerning HCV infections improved, which is confirmed by more frequent anti-HCV testing in groups of increased risk. Assuming the highest recorded annual HCV incidence, not quite 60 thousand patients became diagnosed for HCV infection during last 20 years (from 1993).

Concluding, variability of HCV genotypes prevalence in particular regions of Poland should be stressed. Genotype 1 is predominant as in other European countries. Over the period of recent 10 years frequency of genotype 1 infections increased, whereas genotype 3 and 4 - decreased. Age and HIV co-infection were also demonstrated as factors affecting genotypes distribution. Further studies should be focused on analysis of infection paths with particular HCV genotypes.

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