A Cross-Sectional Epidemiological Study of HBV, HCV, HDV and HEV Prevalence in the SubCarpathian and South-Eastern Regions of Romania

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Abstract

Aim: To evaluate the prevalence of HBV, HCV, HDV and HEV infections in populations with different categories of risk and the seroprevalence of HBV and HCV infections in subjects asking for a medical examination. **Method**: We conducted a cross-sectional, epidemiological study in 2,851 subjects from the SubCarpathian and South-Eastern Romania (including 17 counties, 34% of the country area and 42% of the population). The subjects were divided into four groups: controls (n=2,540, i.e. consecutive subjects asking for a medical examination), subjects with very low risk (students; n=44), with low risk (doctors and nurses; n=93) and with high risk for viral hepatitis (hemodialysis patients; n=174). All subjects were screened for HBsAg, antiHCV and ALT level. In populations at risk, antiHBs, HBeAg, antiHBe, antiHBc (IgG), HBV-DNA, HCV-RNA, antiHDV(IgG) and antiHEV(IgG) were also assessed. **Results**: In controls, HBV seroprevalence was 5.59% and HCV seroprevalence 4.56%. The risk factors for HBV infection were: age, male gender and South-East region of Romania. The risk factors for HCV infection were: age, female gender, elevated ALT level and the South-East region of Romania. In the very low risk population HBV, HCV, HDV and HEV seroprevalence was: 2.27%, 0%, 0% and 12.5%, respectively. In low risk population the seroprevalence was 2.15%, 1.07%, 0% and 13.98%. In hemodialysis patients, HBV and HCV seroprevalence were 7.91%, respectively 39.26%. HCV-RNA was detectable in 20.69% cases. **Conclusion**: In the South and South-Eastern Romania the seroprevalence of viral hepatitis infections is intermediate, similar to other Romanian regions or the Balkans.

Received: 20.08.2009 Accepted: 28.01.2010
J Gastrointestin Liver Dis
March 2010 Vol.19 No 1, 43-48
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Key words

Seroprevalence – HBV – HCV – HDV – HEV – risk factors – epidemiology – hemodialysis.

Introduction

Viral hepatitis infections are still an important health and socioeconomic problem worldwide, despite continued progress in their prevention and treatment. Globalization has erased the borders and put the threat of viral infections on the agenda of all governments. Romania, as a central-east European country, at the cross roads of main routes between Asia and Europe, is exposed to the risk of many types of infections. The periodical evaluation of the epidemiological data is important for a better knowledge of the health status of the populations and for preparing more accurate future health strategies [1-5].

In this cross sectional, observational study we aimed to estimate the prevalence of HBV, HCV, HDV and HEV infections in Romania on a continuous nonselected population from the South and South-Eastern Romania examined between October 1st, 2008 and March 31st, 2009. We also analyzed the differences in prevalence of viral infections between different subject groups stratified by their risk for infection. In the groups at low risk for viral infections we also investigated the prevalence of occult HBV and HCV infections [6].

Material and methods

Study population

The study is a cross sectional epidemiological study involving 2,851 adult subjects from 17 districts of the SubCarpathian (southern from the Carpathians mountains) and South-Eastern regions of Romania, covering an area of 93,047.6 km2 (34% of the territory of Romania) and having a population of 9,262 602 (42% of the population of Romania).

We studied 2,540 subjects seeking a medical examination. This was a heterogeneous population with or without

symptoms interested in a better knowledge about their health status. Some of them (25 %) requested a medical examination for elevated ALT levels.

We also studied subjects belonging to three categories of risk, according to Santantonio et al [1]: very low risk/no risk (casual contact, household contact), low risk (occupational exposure (doctors, nurses, sexual activity with long-term partners), moderate risk (high-risk sexual activity, vertical transmission from mother to child), and high risk (hemodialysis patients, blood transfusion or transplantation recipients before 1992, injection drug users). Our very low risk population (n=44) was represented by students from the"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania. The low risk population (n=93) was represented by doctors and nurses, while the high-risk population was represented by patients on hemodialysis (n=174).

A questionnaire was used to record relevant socio-demographic characteristics of the subjects asking for a medical examination: gender, age, residence (urban vs. rural). For the groups of very low, low and high risk for infection, a more detailed questionnaire was conceived in order to record sex, age, education, marital status, parity, residence (urban vs. country), socioeconomic level, a detailed history of injection and illegal drug use, tattooing and body piercing, and sexual practices.

Methodology

Each subject completed the questionnaire and was examined by a physician. All data were recorded in an electronic chart.

All subjects were screened for HBsAg, anti-HCV antibodies and ALT levels (spectrofotometric method - Roche Diagnostics). For all subjects in the very low-risk, low-risk and high-risk categories a more detailed virusological investigation was performed, including: anti-HBs, HBeAg, anti-HBe, anti-HBc, HBV-DNA, anti-HDV, HCV-RNA and anti-HEV antibodies (IgG).

Serum samples

Serum samples were collected in Synevo Laboratories (Bucharest, Constanta, Craiova and Medgidia) from the 2,851 individuals (1,218 males and 1,633 females; age, 36.80± 9.68 years) between December 1st, 2008 – March 31st, 2009.

About 26 mL of venous blood was collected from each subject (4 EDTA vacutainers for viremia samples, 2 Gel vacutainers for biochemistry and viral markers samples). The blood samples were centrifuged at 4000 rpm for 10 minutes and serum was stored below -80°C (viremia samples). All virusological tests were performed in the Synevo Laboratories or in the Institute fur Medizinische Diagnostik from Hanover, Germany.

HBV markers: HBsAg, anti HBsAb, anti HBc IgG Ab and HBeAg were determined by using commercially available ELISA (ECLIA, Roche Diagnostics). HBV viral load (copies/mL) was determined by quantitative real-time PCR using Cobas TaqMan48 (Roche Diagnostics). **HCV** markers: anti HCV antibodies were determined by ELISA (BIORAD, France). HCV viral load (copies/mL) was determined by quantitative real-time PCR using Cobas TaqMan48 (Roche Diagnostics). **HDV** markers: anti HDV IgG antibodies were determined by ELISA (DRG, Germany). **HEV** markers: anti HEV IgG antibodies were determined by Western Blot assay (recomBlot HEV IgG MIKROGEN GmbH, Martinsrled).

Statistical analysis

The stastical analysis was performed using the SPSS version 15.1 software package (SPSS, Inc., Chicago, IL). Results are expressed as mean ± SEM and proportions. Normality was assessed and *t*-test or a non-parametric test were used for normally and non-normally distributed continuous variables. The means and percentage were calculated and compared between variables using Student *t* and chi-square test, respectively.

Results

Prevalence of hepatitis B and C viruses in population asking for a medical examination

There were 2,540 subjects included in this group ((1,112 males and 1,428 females; mean age 39.7 ± 14.4 years). HBsAg and anti-HCV seropositivity were detected in 5.59% (142/2540; CI:4.7-6.6) and 4.56% (116/2540; CI:3.8-5.5) of subjects, respectively; 6/2,540 (0.24) subjects presented both HBsAg and anti-HCV-antibodies.

The population distribution by age groups in the studied regions of Romania (17 districts) was not very different from our controls asking for medical examination except the youngest (0-19 years) age-groups (Table I). In both populations, about 50% of subjects were younger than 39 years.

Table I. The population distribution by age groups in the SubCarpathian and South-Eastern regions of Romania (17 districts) and in the study group

Age groups	Number	% of total population	% of the 2,540 study subjects
0-9 years	867,452	9.36	3.36
10-19 years	1,317220	14.22	3.36
20-29 years	1,472917	15.90	20.66
30-39 years	1,359825	14.68	23.77
40-49 years	1,319752	14.27	16.45
50-59 years	1,074180	11.59	17.51
60-69 years	985,766	10.64	9.76
70-79 years	726,020	7.83	4.14
80+ years	139,470	1.50	0.98
Total	9,262602	99.99	99.99

The mean age of the HCV-positive population was significantly higher than that of HCV-negative subjects ($p<0.0001$) (Table II). The highest number of anti-HCV positive patients belonged to the 60-69 year age group ($p=0.0227$; OR 1.9780). In the same group the number of

Table II. Mean age, gender and ALT level in the subjects from the general population

	HBsAg +	HBsAg -	p	HCVAb +	HCVAb -	p
Mean age	43.31 ±13.89	40 ± 14.1	0.001	52.32 ± 14.1	39.15 ± 14.13	<0.0001
M/F	91/57	-	0.003	38/78	-	0.002
ALT	48.20 ± 4.56	39.08 ± 4.12	0.059	66.75 ± 6.6	38.39 ± 4.03	<0.0001

HCV positive female subjects was significantly higher than of male subjects (p=0.0019; OR 5.59). More females than males were anti-HCV positive (67.24% vs. 32.76%; p=0.002; OR:1.6) in the entire study population, regardless of the age group. The prevalence of anti-HCV was higher in the South-Eastern region of our country: Constanta (6.37%, p< 0.001; OR 2.15) and Medgidia (7.69% p<0.01; OR 2.64) than in Bucharest (3.05%) and Craiova (3.27%).

The mean age of HBsAg-positive subjects was 43.31±13.89 years, younger than that of anti-HCV-positive subjects (52.32±14.1 years). However, in both groups, the mean age was higher than in subjects without hepatitis B and C markers (p<0.0001) (Table II). More males than females were HbsAg-positive (61.49% vs. 38.51%; p=0.003; OR:2.359). HBsAg-positivity was higher in the 50-59 years age group (10.45%; p=0.0123; OR: 1.97), and not different between males and females (p=0.0987; OR:1.79).

We investigated the geographical distribution of the seroprevalence of hepatitis B and C viruses in three urban areas with a population above 250,000 each (Bucharest, Craiova and Constanta). HBsAg was detected in 4.04%, 7.14% and 6.47% of subjects from these urban areas. Anti-HCV seropositivity was found in 3.05%, 3.27% and 6.37%, respectively. There were significant differences between the three urban areas: Bucharest had the lowest rate of HBV (p=0.02; OR: 1.8) and HCV seroprevalence (p=0.01; OR:1.6), significantly lower than Constanta (p=0.0005; OR: 2.2).

Mean ALT serum levels in HBsAg-positive and –negative subjects were 48.20±4.56 IU/L and 39.08 ±4.12 IU/L, respectively (p=0.059). Mean ALT serum levels were higher in anti-HCV-positive versus HCV–negative (p<0.0001) (Table II). Twenty-seven out of 116 (23.27%) HCV positive subjects had normal ALT levels.

Prevalence of viral B, C, D, and E hepatitis infections in the very low risk population

This group included 44 students (mean age: 22.91±0.56 years; males/females: 13/31). In only 1 out of 44 (2.27%) subjects HBsAg was present (a 23 year old female, normal ALT level). HBV-DNA was negative in all subjects. None of the subjects was anti-HCV or anti-HDV positive. HCV-RNA was negative in all subjects. Anti-HEV were found in 12.5% (5/40) subjects. A high ALT level was found in 3/44 (6.81%) individuals: none was HBV or HCV sero-positive.

Prevalence of viral B, C, D, and E hepatitis infections in the low risk population

The mean age of the 93 doctors and nurses with occupational exposure to hepatitis viruses was 36.71 ± 8.88 years; 91.4 % (85/93) of the subjects were female. HBV, HCV, HDV and HEV seroprevalence rates were 2.15%, 1.07%, 0% and 13.98%, respectively. In HBsAg, anti-HCV and anti-HEV-positive groups, the ratio males/females was 0/2, 0/1 and 1/12. HBsAg-positive patients belonged mainly to the 20-29 years age group and the anti-HCV-positive patients to the 40-49 age group. HBV-DNA was positive in 1 subject (1.2%). HCV-RNA was negative in all subjects, including anti-HCV-positive individuals. None of the subjects had HBV+HDV or HBV+HCV coinfection.

Occult HBV, HCV infection

None of the subjects had occult HBV, HCV infection in the low risk and very low risk populations.

Prevalence of hepatitis B, C, and D viruses in the high risk population

The prevalence of hepatitis viruses was assessed in 174 hemodialysis patients from 6 dialysis centers from the Southern Romania. The mean age of subjects was 53.71 ± 12.71 years; 85/174 (48.85%) were males. Distribution of subjects according to the urban/rural provenience was 90/84.

HBsAg and anti-HCV antibodies were detected in 7.91% and 39.26%, respectively, of the subjects. RNA-HCV was positive in 20.69% individuals. There was a significant difference between HbsAg-positive and HbsAg-negative patients regarding mean age (53.69±12.26 vs. 44.81±14.97, p=0.0133), but not mean ALT level (29.81 ± 2,83 vs. 22.071 ± 2.14; p=0.13). We observed a low prevalence in the 50-59 age group (p=0.02; p=0.01) for HBsAg-positive and anti-HCV-positive patients. There were no differences regarding mean age for anti-HCV-positive compared to anti-HCV-negative patients. Mean ALT level was higher in anti-HCV-positive patients (41.78± 32.5 vs. 15.99±14.09; p=0.0001). Although not statistically significant, more males than females were HBsAg-positive (63.64% vs. 36.36%; p>0.05) and anti-HCV-positive (57.81% vs. 42.19%, p=0.056). More patients from rural areas were HBsAg-positive - 63.64% vs. 36.36% (p>0.05). In anti-HCV-positive patients, repartition in urban and rural areas was equal (50.77% vs. 49.23%, p=0.43). Coinfection HBV+HCV was found in 2/174 patients (0.11%). No hemodialysed patient was anti-HDV positive (Table III).

Discussion

Despite progress in the diagnosis and treatment of viral hepatites, their incidence is still high in some parts of the world. In the context of globalization, which currently facilitates the large-scale spread of disease more than ever, all regions are exposed to the risk of viral infections [3, 4]. The absence of an anti-HCV vaccine amplifies the risk of

Table III. Hepatitis viruses seroprevalence in the population asking for medical examination and in the three categories of subjects at risk

	No. subjects	HBsAg	Anti HCV	Anti HVD	Anti HVE	ALT>2N
Study group	2,540	5.59%	4.56%	-	-	37.69%
Very-low-risk (students)	44	2.27%	0%	0%	12.5%	6.82%
Low-risk (doctors and nurses)	93	2.15%	1.075%	0%	13.98%	4.3%
High-risk (hemodialyzed patients)	174	7.91%	39.26%	0%	-	15%

HCV transmission and explains why the incidence of HCV infection is still increasing all over the world. This is the reason why periodical reevaluation of epidemiologic data is necessary in all countries [7, 8].

Many epidemiological studies have methodological errors which have severely biased the results. The most frequently observed errors result from inadequate sampling size (i.e. too small), or nonhazardous draw of the subjects (inadequate selection criteria) [9]. Sample size can strongly influence the results of a survey. Before starting a survey, it is important to calculate whether the planned sample size is sufficient to detect an effect. Unfortunately, there is a direct relationship between the sample size and the costs of the survey [10]. Many surveys must stop earlier due to financial constraints, having a too small number of subjects evaluated. This is the case of most of the surveys performed in Romania in the 80's on hemodialyzed patients. In other surveys, the authors excluded subjects younger than 18 years [11].

Therefore, statisticians fall between two types of errors: small sample size or incorrect sampling. How can we avoid these errors if the funds or duration of a study are limited? The answer is to reduce the sample size and to randomly choose the subjects of the sample. The sample size is dependent on the presumed frequency of the event and the desired level of accuracy and could be calculated [12]. A disease with a high prevalence such as HBV infection in Taiwan or Hong Kong does not require large sample dimension. On the contrary, the same viral infection in a low-prevalence region such as Northern Europe requires a larger sample dimension and consequently more time and funds. For Romania, with a medium prevalence (3-5%), a 2,000 - 3,000 subjects sample is representative for a region with 9 million inhabitants, provided the proportion of age-groups in the sample is not much different from that in the general population from the area (Table I). We studied consecutive patients seeking medical examination in an established interval of time.

For a better characterization of the risk factors of hepatitis viral infections, we tested the presence of hepatitis viruses in subjects stratified according to the Santantonio classification by the risk of infection [1]. In the high-, low- and very low-risk populations we also evaluated the viral load in subjects with negative serology, in order to detect occult infections. It is well-known that in immuno-compromised patients, for example patients with chronic renal failure who are on hemodialysis, serological tests may be negative even in the context of positive viral loads due to a weak immune response. These patients can spread the infection despite the low level of viremia [13].

HBV prevalence

HBsAg prevalence in our general population was 5.59%, similar to other Balkan countries with intermediate HBV prevalence (Greece 7.3-8%, Albania 5.3-12%, Serbia 4.4-13%, Italy 2.0-5.1%) and lower than in Turkey: 10-13.8% [14-18]. There was a significant difference between male and female gender, with a larger number of HBsAg positive male subjects (p=0.003; OR 2.359), as in other European countries.

HBV prevalence was highest in the 50-59 years age group. In this age group, the risk for a male patient to be HBsAg positive was 1.79 times higher than for a female subject. There were also significant differences regarding HBsAg prevalence among different cities, indicating that the distribution of HBV infection in the surveilled geographical area is irregular, the most affected districts being those with low socio-economic status. Our results are similar to other epidemiological surveys data from our country and from abroad: a recent study from Turkey showed significant differences regarding HBsAg prevalence among different regions - Western 2-4 % , Eastern 4-8%, and South-Eastern Turkey 3.9-12.5 % [19].

HCV prevalence

The prevalence of anti-HCV antibodies in the general population was 4.58%, higher than in others countries (i.e. Greece: 1.95-2.3%, Turkey 0.34%, Italy: 2.4%) [20, 21]. The highest prevalence was registered in the 60-69 years age group. The number of HCV positive females versus males was significantly higher in the entire study population, regardless of the age group. The prevalence of anti-HCV was higher in the South-Eastern Romania (Constanta and Medgidia).

The distribution of HCV infection was also irregular and overlapped with that of HBV infection, HBV and HCV sharing the same geographic areas of high prevalence. These findings confirm that socio-economic status is an important

determinant for the risk of HBV and HCV infections. In these districts, unlike HBV infection, HCV affected more frequently elderly females.

Our data suggest that both HBV and HCV infections were acquired in the past, when population education and the preventive measures had low efficacy.

Hepatitis viral infection prevalence in the very low, low, and high-risk populations

In the very low risk group, the prevalence of HBsAg was low, 2.27%, indicating the efficacy of vaccination and educational programs. No cases of HCV infection were found in this group. This is an important observation which certifies the efficacy of educational measures of prevention [22, 23].

Low prevalence rates of HBV and HCV infections, 2.15% and 1.07%, respectively were found in the low-risk population (medical staff: doctors and nurses). This is not surprising taking into account that for the medical personnel vaccination against HBV is compulsory, while the measures for preventing HCV transmission are strictly enforced.

In the hemodialysed patients (high-risk group) we noted a prevalence rate of HCV infection of 20.69% (PCR) and 39.26% (antiHCV), depending on the method of testing. The serology is associated with problems of specificity and sensitivity in patients on renal replacement therapies [24, 25]. False positive results from polyclonal B cell stimulation in the context of other infections (i.e. HIV) or autoimmune diseases (i.e. systemic lupus erythematosus) can occur in this category of patients. False negative results are also observed in hemodialysis patients; a recent report from Israel indicated that 9% of seronegative hemodialyzed patients had positive HCV-RNA tests using PCR techniques. In hemodialysis patients, HCV seroprevalence is reported differently in several studies: very high in the Eastern region of Romania (Moldavia): 75.0%, in Egypt: 80.0%, in Bulgaria: 65.8% and in Saudi Arabia: 57% or low such as in Belgium: 9.4%, France: 16.3% and Netherlands 3.4%. Similar seroprevalence rates as in our study were found in the USA: 22.3%, Italy: 22.5% and Turkey: 31.4% [26]. It is worth mentioning that in all these studies only old serological tests were used for HCV screening, with low sensitivity and specificity rates, probably due to financial restriction.

The prevalence of HBsAg in the high-risk population of hemodialyzed patients was 7.49%. Other studies have reported lower rates: France 3.7%, Germany 4.6%, Italy 4.3%, Japan 2.1%, Spain 3.1%, USA 2.4% and UK 0% [27]. We found lower prevalence rates in this population compared with other studies from Romania [28]. These differences could be the result of different methodology and use of tests with a low specificity and sensitivity for viral detection.

Conclusion

In the SubCarpathian and South-Eastern regions of Romania, the seroprevalence of hepatitis viruses is higher than in central and western Europe and similar to other countries from the Balkans. The difference between Romania and the rest of Europe is mainly determined by socio-economic factors, the geographic areas of higher prevalence rates being superposable with those with lower socio-economic level.

The prevalence of HBV chronic infection is higher in elderly males, while the prevalence of HCV chronic infection is higher in elderly females, indicating that both infections were acquired mainly in the 1960-1970s (cohort phenomenon).

The highest prevalence of HBV and HCV chronic infections was observed in hemodialyzed patients, while the lowest prevalence rates were observed in young people who benefitted from HBV vaccination and from the educational measures for preventing HBV and HCV transmission.

An important percentage (29.24%) of the subjects with elevated ALT levels was seronegative for HBV and HCV infection, having another etiology of the hepatocytolitic syndrome.

Acknowledgements

We are grateful to Ion Pop (Institute for Public Health Bucharest) for his assistance in the statistical analysis, and to Cristina Mambet, Stefan Georgescu and Maria Stanciu from the Synevo Laboratories, for their professionalism and excellent collaboration.

Conflicts of interest

None to declare.

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