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Original article

The burden and recent epidemiological changes of the chronic hepatitis B and C virus infections in a Greek referral tertiary center

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SUMMARY

We evaluated the main characteristics of 929 consecutive patients with chronic hepatitis B (HBV) and/or C (HCV) virus infection, who represented 79% (929/1177) of patients seen at our liver clinics between 2002-2007 Of the 929 patients, 437 (47%) had chronic HBV infection, 485 (52%) chronic HCV infection and 7 (1%) chronic HBV and HCV co-infection From period A (2002-2004) to B (2005-2007), there was a trend for decrease in chronic HBV cases (50.4% vs 44.7%, P=0.10) with immigrants being responsible for 36.4% (Albanians: 26.3%) of them and being more frequent in period B than A (30.6% vs 41.5%, P=0.022). In chronic hepatitis B (CHB), HBeAg-positive patients, who were more frequently immigrants than HBeAg-negative CHB patients (65.5% vs 29.5%, P<0.001), increased from period A to B (8.0% vs 17.6%, P=0.045). Intravenous drug use was reported by 41.2% of chronic HCV patients with its proportion increasing from period A to B (32.5% vs 47.4%, P=0.001). In conclusion, chronic viral hepatitis is still responsible for the majority (almost 80%0 of patients seen at Greek tertiary centers. Chronic HCV infection seems to represent the commonest cause mainly maintained by increasing numbers of intravenous drug users. There is a trend for decrease of patients with chronic HBV infection with an increasing proportion of immigrants, mostly Albanians, which results in increasing rates of HBeAg-positive CHB.

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Chronic hepatitis B (HBV) and C (HCV) virus infections represent two of the most common aetiologies of chronic liver diseases with their relative prevalence ranging widely from country to country.[1] Two to three decades ago, Greece was considered as a country of intermediate HBV endemicity with an overall prevalence of chronic HBV infection of 3-5%,[2] but more recent studies demonstrated a reduction of hepatitis B surface antigen (HBsAg) prevalence to below 3%.[3-6] In the nineties and after the development of reliable assays for the detection of antibodies against HCV (anti-HCV), Greece was found to be a country of relatively low HCV endemicity with an overall anti-HCV prevalence of below 2%.[4,7] However, additional studies have shown that the anti-HCV prevalence is substantially higher exceeding 10% in some geographic areas[8] and specific high-risk groups.[9] The burden of a chronic disease on the health care system depends not only on the prevalence of this disease in the general population but on the proportion of diagnosed patients as well. The burden of a chronic disease on tertiary centers also depends on the proportion of diagnosed patients who are referred from the primary care setting. In Greece, the majority of chronic HBV and HCV patients are referred to tertiary centers for two main reasons: first, the initial confirmation of diagnosis that may require sophisticated laboratory methods or even liver biopsy cannot be made in the primary care, and second, all types of therapy for such patients are initiated at tertiary centers. In addition, many chronic HBV or HCV patients are directly seen at the outpatient clinics of tertiary centers without previous visits at primary care physicians. To date, the burden of chronic HBV and HCV infections at Greek tertiary centers, which may reflect most of the burden of these diseases in Greece

has not been studied. Moreover, the effects of possible epidemiological changes associated with several factors including the arrival of great numbers of immigrants from countries of higher HBV and HCV endemicity have not been systematically examined. The aim of this retrospective study was to evaluate the burden and possible epidemiological changes of patients with the chronic HBV or HCV infection seen at our outpatient liver clinics during the last six years. In addition, changes in the use of invasive diagnostic procedures, such as liver biopsy, were also determined.

Key words: Hepatitis B, hepatitis C, immigrants, epidemiology

PATIENTS AND METHODS

Patient population

In total, 1177 adult (>14 years old) patients were seen at our outpatient liver clinics between 2002 and 2007. Of them, 929 (79%) patients fulfilled the inclusion criteria of this study, which were established diagnosis of chronic HBV and/or HCV infection and absence of liver malignancy at presentation, liver transplantation or co-infection with human immunodeficiency virus (HIV).

The diagnosis of chronic HBV infection was based on positive HBsAg for at least 6 months. Patients with chronic HBV infection were divided into HBeAg-positive and HBeAg-negative cases according to their HBeAg status. All HBeAg-positive patients were considered to have HBeAg-positive chronic hepatitis B (CHB). Of the HBeAg-negative patients, those with persistently normal alanine aminotransferase (ALT) activity for ≥12 months and baseline serum HBV DNA <20,000 IU/ml were considered as inactive chronic HBV carriers, while those with increased ALT activity on ≥2 separate monthly determinations, serum HBV DNA ≥2,000 IU/mL and/or active histological lesions were considered as cases with HBeAg-negative CHB. All patients with chronic HBV infection and positive anti-HDV (antibodies against hepatitis D virus) were considered as cases with chronic hepatitis D (CHD). Chronic HCV infection was diagnosed in patients with positive anti-HCV and detectable serum HCV RNA. The diagnosis of cirrhosis was based on clinical findings and/or liver histology. Since liver biopsy was not available in all patients, only patients with decompensated liver disease (history of variceal bleeding, ascites, encephalopathy and non-obstructive jaundice with bilirubin >3 mg/dL) were considered to have cirrhosis in this study.

Methods

All epidemiological, anthropometric and laboratory data were collected from the patients' records. The patients were divided into two groups according to the date of their first clinic visit (period A: 2002-2004, period B: 2005-2007).

Commercially available assays were used for all haematological, biochemical and serological determinations. All patients were tested for serum HBsAg, anti-HBc, anti-HBs, HBeAg, anti-HBe, anti-HCV, anti-HDV and anti-HIV by enzyme immunoassays. HBsAg-positive patients were also tested for serum HBV DNA levels by a quantitative polymerase chain reaction (PCR) assay (Amplicor HBV Monitor™ test, Roche Diagnostic Systems, Inc., Branchburg, NJ, USA) with a sensitivity of 400 copies/mL or approximately 80 IU/mL, while anti-HCV positive patients were tested for presence of serum HCV RNA by a qualitative PCR assay (Amplicor, Roche Molecular Diagnostic Systems, Branchburg, NJ, USA) with a sensitivity of 50 IU/mL.

Statistical analysis

All data were analyzed using the statistical package SPSS (version 16.0, SPSS Inc., Chicago, IL). Quantitative variables were expressed as mean values ±standard deviation (SD). Statistical analysis was performed using the t-test and corrected chi-square test or two-tailed Fisher's exact test, when appropriate. A two-tailed P value <0.05 was considered to be statistically significant.

RESULTS

Of the 929 patients, 437 (47%) had chronic HBV infection, 485 (52%) chronic HCV infection and 7 (1%) chronic HBV and HCV co-infection. Immigrants represented 27% of the study population coming mainly from Albania (13.5%) and countries of the ex-Union of Soviet Socialist Republics (USSR) (5%). Decompensated cirrhosis was present in 102 (11%) cases. Regarding the time of first visit, 406 (43.7%) cases were seen in period A (2002-2004) and 523 (56.3%) in period B (2005-2007) representing 80.4% (403/501) and 77.4% (523/676) of all patients seen at our liver clinics in period A and B, respectively.

Patients with chronic HBV compared to those with chronic HCV infection were significantly more frequently immigrants (35.5% vs 19%, P<0.001) and reported less frequently alcohol abuse (7.3% vs 16.5%, P=0.015). The possible source of infection could be identified significantly more frequently in patients with chronic HCV than chronic HBV infection (55% vs 13%, P<0.001). As expected, the majority of the few cases with both chronic HBV and HCV infection were current or past intravenous drug

users. Finally, liver biopsy was performed significantly more frequently in patients with chronic HCV infection than patients with chronic HBV infection (34% vs 22.0%, P<0.001) (Table 1).

Changes in chronic HBV infection

Two hundred and three (46.5%) cases with chronic HBV infection were seen during period A and 234 (53.5%) cases during period B. The proportion of patients with chronic HBV infection decreased from period A to B but the difference did not reach statistical significance (203/403 or 50.4% vs 234/523 or 44.7%, P=0.10). Age and sex distribution, possible sources of infection and BMI did not significantly change between period A and B, but there was a significant increase in the proportion of immigrants among patients with chronic HBV infection (30.5% vs 39.7%, P=0.046). Albanians represented the majority of these immigrants in both periods, but their proportion decreased from period A to B (51/62 or 82.3% vs 60/93 or 64.5%, respectively, P=0.027). The proportion of cases with decompensated cirrhosis among chronic HBV patients did not significantly change. Significantly less patients underwent liver biopsy in period B than A among all chronic HBV patients (34/234 or 14.5% vs 62/203 or 30.5%, P<0.001) (Table 2) or among the 236 patients with CHB or CHD (31/126 or 24.6% vs 61/110 or 55.4%, P<0.001).

Of the 437 patients with chronic HBV infection, 201 (46.8%) were inactive carriers, 219 (50.1%) had CHB and 17 (3.9%) had CHD without significant changes between the two periods (Table 2). Among the 219 patients with CHB, 29 (13.2%) had HBeAg-positive and 190 (86.8%) HBeAg-negative CHB. The proportion of HBeAg-positive CHB cases increased from period A to B among CHB patients (8/100 or 8.0% vs 21/119 or 17.6%, P=0.045) or even

Table 1. Epidemiological characteristics of patients with chronic hepatitis B (HBV) and/or hepatitis C (HCV) infection seen between 2002 and 2007.

Patients characteristic	**Chronic HBV infection** (n=437)	**Chronic HCV infection** (n=485)	**Chronic HBV and HCV infection** (n=7)	**All chronic liver diseases** (N=929)*	P# value
Age, years	43±16	43±15	32±6	44±15	0.76
Male sex, n (%)	251 (57.4)	272 (56.1)	6 (85.7)	529 (56.9)	0.72
Nationality, n (%)					<0.001
Greek	282 (64.5)	393 (81.0)	5 (71.4)	680 (73.2)	
Non-Greek	155 (35.5)	92 (19.0)	2 (28.6)	249 (26.8)	
Albania	*111 (25.4)*	*14 (2.9)*	0	*125 (13.5)*	
Other Balkans	*8 (1.8)*	*11 (2.2)*	0	*19 (2.0)*	
Ex-USSR	*20 (4.6)*	*28 (5.8)*	1 (14.3)	*49 (5.3)*	
Western Europe	*3 (0.7)*	*12 (2.5)*	1 (14.3)	*16 (1.7)*	
Africa	*3 (0.7)*	*19 (3.9)*	0	*22 (2.4)*	
Asia	*10 (2.3)*	*8 (1.7)*	0	*18 (1.9)*	
Alcohol abuse, n (%)	33 (7.3)	80 (16.5)	2 (28.6)	114 (12.3)	0.015
Source of infection, n (%)					<0.001
Unknown	381 (87.1)	221 (45.5)	1 (14.3)	603 (64.9)	
Known	56 (12.9)	264 (54.5)	6 (85.7)	326 (35.1)	
IVDU	4 (0.9)	200 (41.2)	5 (71.4)	209 (22.5)	
Bood transfusion	10 (2.3)	48 (9.9)	1 (14.3)	59 (6.4)	
Sexual contact	6 (1.4)	1 (0.2)	0	7 (0.8)	
Intrafamiliar contact	12 (2.7)	5 (1.0)	0	17 (1.8)	
Vertical transmission	23 (5.3)	0	0	23 (2.5)	
Professional exposure	1 (0.2)	4 (0.8)	0	5 (0.5)	
Renal dialysis	0	6 (1.2)	0	6 (0.6)	
Body mass index, kg/m²	25.0±4.0	25.0±4.3	23.4±2.8	25.0±4.2	0.95
Decompensated cirrhosis, n (%)	44 (10.1)	55 (11.3)	3 (42.9)	102 (11.0)	0.61
Liver biopsy, n (%)	96 (22.0)	163 (33.6)	4 (57.1)	263 (28.3)	<0.001

Quantitative variables are expressed as mean values±standard deviation, USSR: Union of Soviet Socialist Republics, IVDU: intravenous drug use, #P values refer to comparisons between chronic HBV and HCV infection.

Table 2. Epidemiological characteristics of patients with chronic hepatitis B virus (HBV) infection in relation to the date of first visit (Period A: 2002-2004, Period B: 2005-2007).

	Chronic HBV infection		
Patients characteristics	**Period A** (n=203)	**Period B** (n=234)	P value
Age, years	43.3±16.7	43.0±16.0	0.874
Male sex, n (%)	119 (58.6)	132 (56.4)	0.698
Nationality, n (%)			0.046
Greek	141 (69.5)	141 (60.2)	
Non-Greek	62 (30.5)	93 (39.7)	
Albania	*51 (25.1)*	*60 (25.6)*	
Other Balkans	*3 (1.5)*	*5 (2.1)*	
Ex-USSR	*7 (3.5)*	*13 (5.5)*	
Western Europe	*0*	*3 (1.3)*	
Africa	*0*	*3 (1.3)*	
Asia	*1 (0.5)*	*9 (3.8)*	
Alcohol abuse, n (%)	12 (5.9%)	21 (9.0%)	0.277
Source of infection, n (%)			0.664
Unknown	179 (88.2)	202 (86.3)	
Known	24 (11.8)	32 (13.7)	
IVDU	*1 (0.5)*	*3 (1.3)*	
Blood transfusion	*4 (2.0)*	*6 (2.6)*	
Sexual contact	*2 (1.0)*	*4 (1.7)*	
Intrafamiliar contact	*5 (2.5)*	*7 (3.0)*	
Vertical transmission	*12 (5.9)*	*11 (4.7)*	
Professional exposure	*0*	*1 (0.4)*	
Renal dialysis	*0*	*0*	
Body mass index, kg/m²	25.1±4.1	25.0±3.9	0.848
Decompensated cirrhosis, n (%)	21 (10.3)	23 (9.8)	0.875
Liver biopsy, n (%)	62 (30.6)	34 (14.5)	<0.001
Type of disease, n (%)			0.576
Inactive carrier state	93 (45.8)	108 (46.1)	
Chronic hepatitis B	100 (49.3)	119 (50.8)	
HBeAg-positive	*8 (4.0)*	*21 (9.0)*	
HBeAg-negative	*92 (45.3)*	*98 (41.8)*	
Chronic hepatitis D	10 (4.9)	7 (3.1)	

Quantitative variables are expressed as mean values±standard deviation.
USSR: Union of Soviet Socialist Republics, IVDU: intravenous drug use, NA: not applicable.

among all chronic HBV patients (8/203 or 4% vs 21/234 or 9%, P=0.052). HBeAg-positive CHB was significantly more frequent in immigrants than Greek patients with CHB (19/75 or 25.3% vs 10/144 or 6.9%, P<0.001) or with chronic HBV infection (19/155 or 12.2% vs 10/282 or 3.5%, P=0.001). In particular, immigrants were responsible for 4 (50%) of 8 cases with HBeAg-positive CHB during period A and 15 (71%) of 21 such cases during period B (P=0.517). Of the 17 cases with CHD, only 5 (29.4%) were native Greeks, while the majority (12/17 or 70.6%) were immigrants coming mainly from Albania (10/17 or 58.8%).

Changes in chronic HCV infection

Two hundred (41.2%) cases with chronic HCV infection were seen during period A and 285 (58.8%) cases during period B. The proportion of patients with chronic HCV infection increased from period A to B but the difference did not reach statistical significance (200/403 or 49.6% vs 285/523 or 54.5%, P=0.16). The age and sex distribution, BMI and the proportion of immigrants (approximately 19%) were also not significantly different between chronic HCV patients seen during period A and B (Table 3). The majority of immigrants with chronic HCV infection were from countries of the ex-USSR (28/92 or 30.4%) or Africa (19/92 or 20.7%). In contrast to chronic HBV infection, Albanians represented a minority of immigrants with chronic HCV infection (14/92 or 15.2%). The proportion of chronic HCV patients with identifiable source of infection significantly increased from period A to B (45.5% vs

60.7%, P=0.001) and this was due to the increase of patients infected by intravenous drug use (IVDU). In particular, although IVDU was responsible for the majority of cases with known source of infection in both periods (65/91 or 71.4% vs 135/173 or 78.0%, P=0.299), the proportion of intravenous drug users among chronic HCV patients significantly increased from period A to B (65/200 or 32.5% vs 135/285 or 47.4%, P=0.001).

The proportion of chronic HCV patients with decompensated cirrhosis at presentation did not significantly change from period A to B (14.0% vs 9.5%, P=0.146). In contrast, there was a significant reduction in the proportion of chronic HCV patients who underwent liver biopsy from period A to B (50.5% vs 21.7%, P<0.001) (Table 3).

DISCUSSION

Despite the recent reports of decline in the prevalence of chronic HBV and perhaps HCV infection in Greece,[3-7] chronic infections with these hepatitis viruses are still responsible for the majority of cases seen at the outpatient liver clinics of Greek tertiary centers. In our study, such cases were found to be responsible for almost 80% of all cases seen at our clinics over the last six years. Chronic HCV infection represented the greatest group being responsible for 52-53% of the study population. The predominance of patients with chronic HCV infection among those with CLD is in contrast with the findings of a previous study from our liver unit in the early nineties, in which chronic HCV infection was responsible for approximately 25% of cases with CLD.[10] These data may be related to both increasing relative prevalence and increasing diagnosis of patients with chronic HCV infection in Greece over the last decade.

Our data suggest that there was a trend for decline in the proportion of new cases with chronic HBV infection over the last three years of our study period (from 50% to 45%). This might be due to the reported declining prevalence of

Table 3. Epidemiological characteristics of patients with chronic hepatitis C virus (HCV) infection in relation to the date of first visit (Period A: 2002-2004, Period B: 2005-2007).

	Chronic HCV infection		
Patients characteristics	**Period A** (n=200)	**Period B** (n=285)	P value
Age, years	43.8±14.7	42.1±14.7	0.228
Male sex, n (%)	105 (52.5)	167 (58.5)	0.183
Nationality, n (%)			0.825
Greek	163 (81.5)	230 (80.7)	
Non-Greek	37 (18.5)	55 (19.3)	
Albania	*5 (2.5)*	*9 (3.1)*	
Other Balkans	*4 (2.0)*	*7 (2.4)*	
Ex-USSR	*10 (5.0)*	*18 (6.3)*	
Western Europe	*6 (3.0)*	*6 (2.1)*	
Africa	*7 (3.5)*	*12 (4.2)*	
Asia	*5 (2.5)*	*3 (1.0)*	
Alcohol abuse, n (%)	29 (14.5%)	51 (17.9%)	0.384
Source of infection, n (%)			0.001
Unknown	109 (52.5)	112 (39.3)	
Known	91 (45.5)	173 (60.7)	
IVDU	*65 (32.5)*	*135 (47.3)*	
Blood transfusion	*19 (9.5)*	*29 (10.2)*	
Sexual contact	*1 (0.5)*	*0 (0)*	
Intrafamiliar contact	*1 (0.5)*	*4 (1.4)*	
Vertical transmission	*0*	*0*	
Professional exposure	*1 (0.5)*	*3 (1.1)*	
Renal dialysis	*4 (2.0)*	*2 (0.7)*	
Body mass index, kg/m²	25.6±4.7	24.6±4.0	0.065
Decompensated cirrhosis, n (%)	28 (14.0)	27 (9.5)	0.146
Liver biopsy, n (%)	101 (50.5)	62 (21.7)	<0.001

Quantitative variables are expressed as mean values±standard deviation.
USSR: Union of Soviet Socialist Republics, IVDU: intravenous drug use, NA: not applicable.

chronic HBV infection in Greece,[3-6] which is probably associated with the improvements of the socioeconomic status and the immunization policy in our country over the last decades. Similar changes of HBV epidemiology have been observed in many other European countries.[11] The reduction of the proportion of new chronic HBV patients at our center would have been greater if immigrants, who were more frequent among chronic HBV patients compared to any other group, were excluded. In fact, immigrants were found to represent an important reservoir of newly diagnosed chronic HBV patients with their proportion in our chronic HBV patients increasing from the first to the second period of our study (from 30.5% to 39.7%, P=0.046). The majority of these immigrants were from Albania, which is a country of high HBV endemicity.[12-14] However, the proportion of Albanians among immigrants with chronic HBV infection declined from the first to the second period of our study (from 82% to 64.5%, P=0.027), while the relative proportion of immigrants from other countries (such as ex-USSR and Asian) increased. Taking into account our data as well as the high prevalence of chronic HBV infection in such populations and the fact that they now represent more than 10% of the Greek population,[15] immigrants are not only responsible for a high percentage but they may be responsible for most of the burden from chronic HBV infection in Greece in the near future.

Immigrants not only maintain the burden but may also change the characteristics of chronic HBV infection in our country. In fact, the proportion of HBeAg-positive cases among CHB patients was 8% in the first period, which is in agreement with what is considered to be such a prevalence in Greece (<10%),[16] while it significantly increased to almost 18% in the second period of our study (P=0.045). This was clearly associated with the increase of immigrants, since HBeAg-positive CHB was more frequent among them compared to Greek patients (25% vs 7%, P<0.001). In addition, immigrants were responsible for the majority of HBeAg-positive CHB in both periods of our study (50%-71%). The proportion of cases with CHD (3.9%) among our chronic HBV patients was relatively lower compared to the reported prevalence of HDV infection in other countries of the Mediterranean basin and South-Eastern Europe, where infection is thought to be endemic,[17,18] and similar to the rate of infection among HBsAg-positive blood donors in the United States (3.8%).[19] Immigrants were responsible for the majority (12/17 or 70.6%) of our cases with CHD without significant change over the six years of this study. The high proportion of Albanians (58.8%) among patients with CHD is in agreement to the high HDV prevalence previously identified in Albania.[20]

The proportion of new patients with chronic HCV infection did significantly changed over the six years of our study. The lower proportion of immigrants among chronic HCV than HBV patients (19% vs 36%, P<0.001) is probably associated with the lower prevalence of HCV than HBV among the Albanians,[12] who represent the largest group of immigrants in Greece. In contrast to chronic HBV infection, the majority (51%) of immigrants with chronic HCV infection were from countries of the ex-USSR or Africa, mostly Egypt. There were no significant changes in most of the characteristics of chronic HCV patients, except for the source of infection. In fact, the proportion of chronic HCV patients with identifiable source of infection increased from the first to the second period of our study due to the increase of intravenous drug users (from 32% to 47%, P=0.001). Thus, IVDU, which represents by far the most common source of HCV transmission in Greece, may be now responsible for almost half of our chronic HCV cases. The high proportion of intravenous drug users may be also responsible for the greater proportion of alcohol abuse among chronic HCV than HBV patients

Another interesting finding was that the proportion of patients undergoing liver biopsy decreased for the first to the second period of our study. Such a decrease was statistically significant for both patients with chronic HBV and HCV infection. The decreasing frequency of use of liver biopsies in such patients may be associated with several reasons including increasing ethical considerations about the effect of liver histological findings on the patients' management, decreasing absolute indications in specific settings[21] and increasing use of recent non-invasive techniques that satisfactorily estimate the severity of liver histological lesions and mostly of fibrosis.[22]

In conclusion, our data suggest that chronic viral hepatitis is still responsible for the majority of patients seen at Greek tertiary centers. Chronic HCV infection seems to be the most common cause of newly diagnosed cases of chronic viral hepatitis in recent years mainly maintained by increasing numbers of infected intravenous drug users. There is a relative decrease of patients with chronic HBV infection with a significantly increasing proportion of immigrants, mostly Albanians, among them. The latter phenomenon results in increasing rates of HBeAg-positive CHB with HBeAg-positive patients exceeding 15% of CHB cases in recent years.

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