JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Seroprevalence of hepatitis A,B, and C viruses in Turkish alcoholic cirrhotics and the impact of hepatitis B on clinical profile

Fatih Tekin[1], Fulya Gunsar[1], Elvan Isik Erdogan[1], Ruchan Yazan Sertoz[2], Zeki Karasu[1], Galip Ersoz[1], Omer Ozutemiz[1], Ulus Akarca[1]

[1] *Department of Gastroenterology, Ege University Medical School, Izmir, Turkey*
[2] *Clinical Microbiology, Ege University Medical School, Izmir, Turkey*

Abstract

Introduction: The aims of this study were to detect the seroprevalence of hepatitis A, B, and C viruses in Turkish alcoholic cirrhotics, and to evaluate the impact of hepatitis B infection on clinical profile at first admittance.

Methodology: Serological markers for hepatitis A, B, and C viruses in 300 alcoholic cirrhotics diagnosed between January 1994 and December 2012 were retrospectively reviewed. Among them, 148 eligible patients were divided into group 1 (HBsAg positive, n = 43) and group 2 (HBsAg and anti-HBc negative, n = 105). Clinical characteristics at first admittance of groups 1 and 2 were compared.

Results: The seroprevalence of anti-HAV total, HBsAg, and anti-HCV was found to be 91.5%, 16.3%, and 8.2%, respectively. The prevalence of hepatocellular carcinoma was higher in the HbsAg-positive group compared to HbsAg- and anti-HBc-negative group (16.3% vs. 2.9%, p = 0.007). Other clinical features were similar in the two groups.

Conclusions: Alcoholic cirrhotics have higher frequencies of HBsAg and anti-HCV than the general population. These patients should be investigated for coexistent HBV and HCV infections, and HBV vaccination should not be neglected. Alcoholic cirrhotic patients with concomitant HBV infection should be closely screened for hepatocellular carcinoma.

Key words: alcoholic cirrhosis; viral hepatitis; seroprevalence, Turkey.

J Infect Dev Ctries 2015; 9(3):254-258. doi:10.3855/jidc.6002

(Received 03 October 2014 – Accepted 09 December 2014)

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Introduction

Alcohol consumption is responsible for 3.8% of global mortality [1], and alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease in Europe [2]. The European Status Report on Alcohol and Health 2010 revealed that per capita consumption of alcohol was calculated to be 12.2 liters/year in Europe and 3.4 litres/year in Turkey [3]. Alcohol is long known to be one of the important etiological factors for cirrhosis in Turkey [4]. On the other hand, many studies have shown the synergistic effect of hepatitis C virus (HCV) [5,6] and hepatitis B virus (HBV) [7-12] infections with alcohol consumption in the development and progression of chronic liver disease. Despite its significant importance, there is a lack of data about concomitant HBV/HCV infections in Turkish alcoholic cirrhotics. In this study, we aimed to detect the seroprevalence of hepatitis A, B, and C in alcoholic cirrhotics, and to evaluate the impact of HBV infection on clinical profile at first admittance.

Methodology

Patients

The records of 1,246 patients with documented ALD at the hospital of Ege University Medical School, Izmir, Turkey, between January 1994 and December 2012 were reviewed. Patients' data were obtained from their medical files at the hepatology outpatient clinic. Patients with steatosis, steatohepatitis, alcoholic hepatitis, and acute viral hepatitis A, B, or C were excluded. Patients with incomplete data about the serological markers were also excluded. A total of 300 alcoholic cirrhotics were enrolled in the study. Serological markers for hepatitis A, B, and C in 300 alcoholic cirrhotics were reviewed.

Among 300 alcoholic cirrhotics, 152 patients were excluded from the next part of the study, which aimed to evaluate the impact of HBV infection on clinical profile at first admittance. The reasons for exclusions were the positivity of anti-HBc, anti-HCV, and anti-delta. Patients with incomplete data about their clinical characteristics were also excluded. Overall, 148 eligible patients were included into the study and were

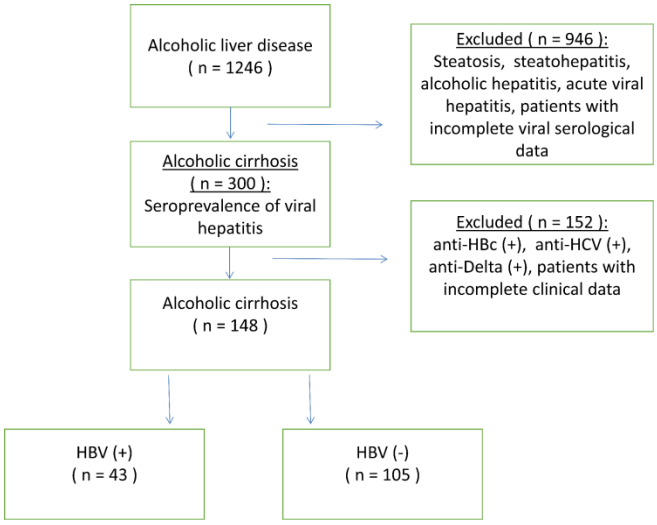
divided into two groups (HbsAg-positive group versus HbsAg- and anti-HBc-negative group). Clinical characteristics of the two groups at first admittance were compared. A flowchart of the study is shown in Figure 1.

Diagnostic criteria for alcoholic cirrhosis included alcohol consumption ≥ 40 gr/day for longer than 10 years; signs of advanced liver disease including jaundice, hepatic encephalopathy, ascites, portal hypertensive bleeding, or splenomegaly; the presence of laboratory abnormalities such as low serum albumin, and/or prolonged prothrombin time; and the presence of radiologic features of cirrhosis such as a nodular liver surface, ascites, or splenomegaly. Hepatocellular carcinoma (HCC) was diagnosed by a combination of elevated serum alfa-fetoprotein levels, and the appearance of liver lesion(s) on radiologic imaging with typical characteristics for HCC [13].

Viral marker assays

HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc-IgG (total), anti-HAV (total), and anti-HCV were measured by enzyme-linked immunosorbent assay (ELISA) with AxSYM analyzer (Abbott, Wiesbaden, Germany) before 2009, and with Architect (Abbott) after 2009. Total anti-HDV antibody levels were measured by ELISA with Murex (Abbott). HCV-RNA was quantitatively detected with VERSANT HCV-RNA 3.0 assay bDNA (Bayer Diagnostics, Berkeley, California, USA.), and the COBAS TaqMan (Roche Diagnostics, Branchburg, USA). Delta-RNA was studied using a Qiagen RNA kit (Qiagen, Hilden, Germany). HBV DNA levels were determined by solution hybridization technique before 2002, and by quantitative polymerase chain reaction (PCR) assay (Abbott RealTime HBV Quantification kit) after 2002, the latter with a detection limit of 100 copies/mL.

Figure 1: Flowchart of the study



Statistical analysis

Differences in proportion of categorical parameters between HbsAg-positive and HbsAg-negative patients were tested using the Chi-square test and Fisher's exact test when necessary. Continuous paremeters were tested using Student's *t*-test if they had normal distribution, otherwise the Mann-Whitney U test was applied. A p value of less than 0.05 was accepted as statistically significant.

Results

Among 300 alcoholic cirrhotics, the positivity of anti-HAV-total, HbsAg, and anti-HCV was found to be 91.5%, 16.3%, and 8.2%, respectively. Among the 23 anti-HCV-positive patients, HCV-RNA was studied in 17 patients and was positive in 14 (82.4%) of them (Table 1). HbsAg was positive in 49 patients, and the positivity of HBeAg, HBV-DNA, anti-delta, and anti-

Table 1. Viral serological markers of alcoholic cirrhotic patients (n = 300)

Serological marker	Data available n (%)	Positive n (%)
Anti-HAV total	188 (62.7)	172 (91.5)
Anti-HCV	280 (93.3)	23 (8.2)
HCV-RNA in anti-HCV positives	17 (74)	14 (82.4)
HBsAg in anti-HCV positives	23 (100)	1 (4.3)
HBsAg	300 (100)	49 (16.3)
HBV-DNA in HBsAg positives	29 (59)	12 (41.4)
HBeAg in HBsAg positives	43 (87.8)	7 (16.3)
Anti-delta in HBsAg positives	21 (42.9)	2 (9.5)
Anti-HCV in HBsAg positives	43 (87.8)	1 (2.3)

HCV in these patients was found to be 16.3%, 41.4%, 9.5%, and 2.3%, respectively (Table 1). Table 2 shows the detailed results of anti-HBs and anti-HBc tests in 251 HbsAg-negative individuals.

Table 3 provides the baseline demographic profiles and clinical characteristics of the study population (n = 148). There were no significant differences in age, gender, daily intake of alcohol, lifetime duration of drinking, smoking history, albumin, total bilirubin, prothrombin time, platelet count, creatinine values, presence of ascites, hepatic encephalopathy, Child-Pugh score, Child-Pugh class, and esophageal variceal bleeding between HbsAg-positive and -negative groups. A total of 10 patients were diagnosed with HCC, 7 (16.3%) in the HbsAg-positive group, and 3 (2.9%) in the HBsAg and anti-HBc-negative group (p = 0.007).

Discussion

A recent population-based, multicenter, national study from Turkey showed that the seroprevalence of HBsAg, anti-HAV total, and anti-HCV was 4.0%, 93.2%, and 1.0%, respectively [14]. The present study showed that both of the seroprevalences of HBsAg (16.3%) and anti-HCV (8.2%) in alcoholic cirrhotics were higher than in the general population. To our knowledge, these data in Turkish alcoholic cirrhotics were not documented in the English literature before. Our data emphasizes the importance of investigation for possible coexistent HBV and HCV infections, and also for HBV vaccination in alcoholic cirrhotics. In our study, the seroprevalence of anti-HAV total was found to be 91.5%. However, the present study does not include data about the ratio of patients who received a hepatitis A vaccine and patients with immunity to HAV due to past infection. On the other hand, a national Turkish study [14] revealed that seroprevalence of anti-HAV-total was 93.2%, whereas only 5.8% of the study population had a HAV vaccination history. Thus, we can speculate that the majority of patients with anti-HAV total positivity had a natural immunity due to past infection.

Table 2. Viral serological markers of HBsAg negative patients (n = 251)

Serological marker	n (%)
anti-HBs: negative / anti-HBc: negative	108 (43)
anti-HBs: negative / anti-HBc: positive	26 (10.3)
anti-HBs: negative / anti-HBc: no data	8 (3.2)
anti-HBs: positive / anti-HBc: positive	65 (25.9)
anti-HBs: positive / anti-HBc: negative	14 (5.6)
anti-HBs: positive / anti-HBc: no data	22 (8.8)
anti-HBs: no data / anti-HBc: no data	8 (3.2)

Table 3. Baseline demographic profiles and clinical characteristics of the study groups

Variables	Alcoholic cirrhosis (Overall) (n = 148)	Alcoholic cirrhosis (HBV+) (n = 43)	Alcoholic cirrhosis (HBV-) (n = 105)	P value
Age (years) (mean ± SD)	51.5 ± 8.9	50.4 ± 8.0	52.0 ± 9.2	ns
Gender (male / female)	143 / 5	43 / 0	100 / 5	ns
Albumin (g / L) (mean ± SD)	3.27 ± 0.72	3.13 ± 0.79	3.33 ± 0.69	ns
Total bilirubin (mg / dL) (mean ± SD)	3.5 ± 4.2	2.9 ± 2.4	3.7 ± 4.7	ns
Creatinine (mg / dL) (mean ± SD)	0.97 ± 0.36	1.01 ± 0.42	0.96 ± 0.34	ns
Platelet ($\times 10^9$ / L) (mean ± SD)	143 ± 80	129 ± 70	148 ± 83	ns
Prothrombin time (seconds) (mean ± SD)	16.5 ± 3.6	17.2 ± 3.4	16.2 ± 3.7	ns
Ascites n (%)	71 (48)	21 (49)	50 (48)	ns
Hepatic encephalopathy n (%)	21 (14.2)	5 (11.6)	16 (15.2)	ns
Child-Pugh score (mean ± s.d.)	8.1 ± 2.1	8.5 ± 2.3	7.9 ± 2.0	ns
Child-Pugh class A / B / C	41 / 71 / 36	9 / 19 / 15	32 / 52 / 21	ns
Esophageal variceal bleeding n (%)	13 (8.8)	6 (14.0)	7 (6.7)	ns
Hepatocellular carcinoma n (%)	10 (6.8)	7 (16.3)	3 (2.9)	0.007

ns: not significant

In the further part of the study, we aimed to evaluate the impact of HBV infection on clinical profile at first admittance. There were no significant differences in clinical characteristics between two groups except the presence of HCC (Table 3). The prevalence of HCC was higher in the HbsAg-positive group compared to HbsAg- and anti-HBc-negative groups (16.3% vs. 2.9%, p = 0.007). To the best of our knowledge, this finding in Turkish alcoholic cirrhotics had not previously been reported in the literature. This result was consistent with previous studies that found the synergistic effect of alcoholism and viral hepatitis infection on the increasing incidence of HCC [7-9,15-17]. In a multicenter study including 207 patients that aimed to investigate the risk factors for HCC in Turkey, the authors revealed that among 33 patients with a history of heavy alcohol intake, 18 had concomitant chronic viral hepatitis infection, and alcohol alone was the etiology of HCC in only 15 cases (7.2%) [18].

It is generally acknowledged that HBV is involved in the development of HCC through long-term chronic infection [19]. However, we did not know the exposure time of HBV infection in our patients. Furthermore, our data showed the prevalence of HCC only at the time of admission, and surveillance data of the patients, including possible newly developed HCC, were not included in this study. Another limitation of the study was that its retrospective nature may have resulted in unintentional bias; in addition, subanalysis of HCC patients was not performed due to a small number of patients with HCC.

Among 300 alcoholic cirrhotics, 152 patients were excluded from the second part of the study, which aimed to evaluate the impact of HBV infection on clinical profile. One of the exclusion criteria was the positivity of anti-HBc in HbsAg-negative patients. The presence of anti-HBc without HBsAg might indicate previous exposure to and recovery from HBV or the presence of occult HBV infection. Recently, two studies reported that anti-HBc positivity without HBsAg was a risk factor for the development of HCC [20], and was associated with more advanced liver disease in patients with alcoholic cirrhosis [21].

Conclusions

Alcoholic cirrhotics were found to have higher frequencies of HBsAg and anti-HCV than the general population. These patients should be investigated for coexistent HBV and HCV infections, and HBV vaccination should not be neglected. Alcoholic cirrhotic patients with concomitant HBV infection have higher rates of HCC than do those with alcoholism alone at first admittance. Alcoholic cirrhotic patients with concomitant HBV infection should be closely screened for HCC.

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Corresponding author

Dr. Fatih Tekin
Ege Universitesi Tip Fakultesi
Gastroenteroloji Bilim Dali, Bornova
35100, Izmir, Turkey
Phone: +90-232-3904357
Fax: +90-232-3427764
Email: drtekinfatih@gmail.com

Conflict of interests: No conflict of interests is declared.