ETIOLOGICAL DISTRIBUTION AND CLINICAL FEATURES OF CIRRHOTIC PATIENTS: SINGLE TERTIARY REFERRAL CENTER EXPERIENCE

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ABSTRACT

Introduction: Cirrhosis has various etiologies, and the etiologic distribution differs from center to center. Our aim is to reveal the etiological distribution and clinical features of cirrhotic patients.

Materials and methods: We retrospectively recruited 1144 patients. Of patients, 480 were cirrhotic, 664 were non-cirrhotic. Patients were diagnosed by means of clinical features, laboratory values, radiologic imaging and biopsy when required.

Results: Of the 480 cirrhotic patients, 250 were male (52%), and the mean age was 57.6 years. In cirrhotics, 289 (60.2%) patients were decompensated. However, hepatitis B virus (HBV) - hepatitis C virus (HCV) coinfection and Budd-Chiari syndrome were found to have highest tendency of decompensation (85.7%, 84.6% respectively). Child-Pugh classification was evaluated: 243 (50.6%) class A, 164 (34.2%) class B and 73 (15.2%) class C patients were analyzed. Ascites in 206 (42.9%), hepatic encephalopathy in 55 (11.4%), hepatocellular carcinoma in 23 (4.7%), and spontaneous bacterial peritonitis in 17 (3.5%) of the patients were determined. In the group of patients with viral etiology, while 160 (53.9%) of 297 cirrhotic patients were HCV, 137 (46.1%) were HBV, 503 (75.8%) out of 664 non-cirrhotics were HBV and 161 (24.2%) were HCV infected.

Conclusion: Although HBV was more common in chronic hepatitides, cirrhosis was mostly caused by HCV infection. The reason of this may be due to anti-viral use for HBV. We found that decompensation rate was higher for Budd-Chiari syndrome and HBV-HCV coinfected patients. Cryptogenic cirrhosis still continues to have high prevalence. The reason for this may be undiagnosed autoimmune liver disease, non-alcoholic steatohepatitis, occult HBV or gluten enteropathy.

Key words: Cirrhosis, etiology, viral hepatitis.

DOI: 10.19193/0393-6384_2016_3_73

Received June 30, 2015; Accepted January 02, 2016

Introduction

Cirrhosis is a progressive and fatal disease that impairs the morphological structure of the liver, and it develops on the basis of chronic liver disease; it is characterized by the hepatocellular necrosis, widespread fibrosis and nodule formation, vascular disorganization, regenerative stimulation and tendency to neoplasia(1). In the United States of America (USA), 35,000 people die each year due to liver cirrhosis, and this disease is the 10th mortality reason in men, and the 12th in women(2). Besides leading to early deaths, cirrhosis causes patients to suffer a lot, and it is also the reasons of labor loss and high health expenses; the disease is therefore a cause of important losses for the patients(2,3).

After the cirrhotic changes have started to exist in a liver cirrhosis, fibrotic process progresses in a similar way whatever the underlying etiological reason is, and in an established cirrhosis, it is almost impossible to determine the etiological reason histopathologically.

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Progression to cirrhosis has fortunately slowed down considerably, due to development of the new treatment modalities, and the follow-up of patients in light of the internationally accepted guides during the period of hepatitis.

Child-Pugh and model of end stage liver disease (MELD) scoring systems are currently used in cirrhotic patients, in determination of the disease severity, its prognosis and survival. MELD scoring system is being used more frequently, especially in the patients who are planned to undergo transplantation. Clinical features and staging are also important regarding the follow-up and treatment of the disease, and also the determination of its prognosis. After development of the decompensation signs like ascites, jaundice, esophageal variceal hemorrhage, and hepatic encephalopathy, survival rate in cirrhosis decreases\(^{(4,5)}\).

Primary reasons leading to cirrhosis are viral hepatitis and use of alcohol all over the world; however many other reasons play role in the etiology. Rapidly developing research techniques help the clinicians in revealing the etiology of cirrhosis; however cirrhosis with unknown etiology (cryptogenic) still exist frequently in the clinical practice. Many studies report that the rate of cryptogenic cirrhosis averages between 3% and 10%\(^{(6-8)}\). As it is a fact all over the world, etiological distribution of the cases with cirrhosis in our country also shows regional differences\(^{(9)}\).

Patients in the regional cities also apply to our hospital, and it is a health center with a high patient turnover; therefore etiological percentages of the cases followed-up in the hepatology clinic, provide an important information about the etiological factors of cirrhosis existing in this district. We aimed to indicate the etiological distribution of the cases with cirrhosis in our hospital that is a tertiary center including transplantation applications also; we additionally considered to evaluate the clinical features of these patients, and to investigate the complications.

Materials and methods

**Patients**

A total of 1312 patients with chronic liver disease were investigated retrospectively; the cases were those who had applied to the Gaziantep University Medical School Hospital Hepatology clinic, between the years from 2009 to 2014. The patients were initially separated to two groups, as the cases with cirrhosis or non-cirrhotic chronic liver disease. Etiological distributions and clinical features of the patients with cirrhosis were evaluated, and the complications were determined. The study was carried out in accordance with the principles of the revised 2013 version of the Declaration of Helsinki of 1975, with the approval numbered 18.05.2015/160 of University of Gaziantep Faculty of Medicine Clinical Research Ethics Committee.

**Diagnostic criteria**

Diagnostic criteria used for the diagnosis of liver cirrhosis were as follows:

- Signs in accordance with cirrhosis in the laboratory analyses; low albumin level, AST/ALT ratio >1, inversion of albumin/globulin ratio, presence of thrombocytopenia, and prolonged prothrombin time.

- Imaging findings [ultrasonography (USG) and/or computed tomography (CT)]; decrease in the liver size, parenchymal heterogeneity, superficial nodular changes, hypertrophy of the left lobe, and splenomegaly.

- Clinical/endoscopic signs suggestive of cirrhosis; esophageal varices, ascites, hepatic encephalopathy.

Development of ascites, hepatic encephalopathy, jaundice or gastrointestinal bleeding in the cirrhotic patients were accepted as signs of decompensation.

After exclusion of all other etiological reasons in the patients with cirrhosis, cirrhosis related with non-alcoholic steatohepatitis (NASH) was diagnosed clinically by the existence of obesity, diabetes and hyperlipidemia, and also their association with the ultrasonographic findings of diffuse echogenicity increase in the liver.

Besides hematological, biochemical, serological, immunological, radiological and endoscopic analyses needed for diagnosis and etiological evaluation, hepatic liver biopsy was performed in appropriate cases. Non-cirrhotic cases were thus excluded, and 480 patients with cirrhosis were included in the study for being compared regarding their demographic and clinical characteristics. Included patients were evaluated for the demographic data, the parameters indicating disease severity (Child-Pugh score and MELD score), and the complications; obtained data were noted down.

Complications of cirrhosis were diagnosed by evaluating clinical and laboratory findings. Spontaneous bacterial peritonitis was diagnosed by
evaluating the ascites culture, and the number of polymorphonuclear leukocytes in the ascites fluid. Hepatic encephalopathy was diagnosed clinically, after excluding the other causes of encephalopathy. Hepatorenal syndrome was diagnosed by considering the diagnostic criteria included in the European Association for the Study of the Liver (EASL) guidelines 2010\(^\text{(10)}\). Portopulmonary hypertension was diagnosed by considering the last updated diagnostic criteria related with this subject\(^\text{(11)}\).

**Statistical analysis**

Statistical analyses were performed using licensed Statistical Package for the Social Sciences (SPSS) software (version 15.0, SPSS Inc., Chicago, IL, USA). Statistical significance of the relation between two variables was evaluated using the Chi-square test. A p value < or =0.05 was accepted to be significant.

**Results**

Of the 480 cases investigated, 250 were men and 230 were women. The mean age of the cases was determined to be 57.6 ± 13.27 years. When the etiologic distribution was assessed, hepatitis C virus (HCV) was found to be the most frequent etiology with a rate of 33.3%, which was followed by hepatitis B virus (HBV) with 28.5%, cryptogenic cirrhosis with 18.7%, and alcohol and primary biliary cirrhosis with 3.7% (Table 1).

Of the patients, 289 were in the decompensated phase (39.8%); a majority of decompensated cirrhotic cases existed with the following etiologies: HBV and HCV association, Budd-Chiari, alcohol, and cryptogenic (Figure 1).

**Figure 1:** Decompensation rates of diseases of cirrhosis etiology.

HBV; hepatitis B virus, HCV; hepatitis C virus

The patients were distributed according to the Child-Pugh staging, as follows: Stage A 243 (50.6%), Stage B 164 (34.2%), and Stage C 73 (15.2%).

When complications of cirrhosis were investigated, their frequencies were determined as follows: ascites in 206 patients (42.9%), 55 cases with hepatic encephalopathy (11.4%), hepatocellular cancer in 23 patients (4.7%), and spontaneous bacterial peritonitis in 17 patients (3.5%).

As illustrated in the column of other complications in the table, the remaining complications were distributed as follows: of the 3 patients with HBV, 2 had portopulmonary hypertension, and one had portal venous thrombosis; of the 5 patients with HCV, one had hepatorenal syndrome, 3 had portal venous thrombosis, and one had portopulmonary hypertension; portal venous thrombosis in one patient with primary biliary cirrhosis (PBC); portal venous thrombosis in one case with alcohol consumption; hepatorenal syndrome in one patient with Budd-Chiari; of the 5 patients with cryptogenic cirrhosis, 4 had portal venous thrombosis, and one had hepatorenal syndrome.

Of the patients, 289 were in the decompensated phase (60.2%), and 191 were in the compensated phase (39.8%); a majority of decompensated cirrhotic cases existed with the following etiologies: HBV and HCV association, Budd-Chiari, alcohol, and cryptogenic (Figure 1).

**Table 1:** The distribution of causes of cirrhosis.

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<thead>
<tr>
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<tr>
<td>HCV</td>
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<tr>
<td>Wilson’s disease</td>
<td>11 (2.2)</td>
</tr>
<tr>
<td>Others*</td>
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</tr>
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</table>

*Non-alcoholic steatohepatitis (NASH), autoimmune liver disease, HBV+HCV, Hemochromatosis

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patients received telbivudine (3.6%), 21 patients received entecavir (15.3%), and 58 patients received tenofovir (42.3%); 26 patients did not receive antiviral therapy (18.9%) because of the HBV DNA negativity. Demographic characteristics of the patients, their disease severities, and distribution of complications are illustrated in Table 2.

Table 2: The etiologies, demographic and clinical features and complications of cirrhosis patients.

<table>
<thead>
<tr>
<th>Etiology (n=480)</th>
<th>Patients n (%)</th>
<th>Female n (%)</th>
<th>Age</th>
<th>Child-Pugh score</th>
<th>MELD (Median)</th>
<th>Varices</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A n (%)</td>
<td>B n (%)</td>
<td>C n (%)</td>
<td>Grade 1 n (%)</td>
<td>Grade 2 n (%)</td>
<td>Grade 3 n (%)</td>
<td>Asches n (%)</td>
</tr>
<tr>
<td>HCV</td>
<td>160 (33.3)</td>
<td>97 (60)</td>
<td>63 (44)</td>
<td>67 (54)</td>
<td>53 (33)</td>
<td>20 (13)</td>
<td>10</td>
</tr>
<tr>
<td>HBV</td>
<td>137 (28.5)</td>
<td>35 (26)</td>
<td>56 (47)</td>
<td>49 (35)</td>
<td>24 (18)</td>
<td>11 (8)</td>
<td>9</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>90 (18.7)</td>
<td>57 (63)</td>
<td>35 (47)</td>
<td>36 (40)</td>
<td>11 (12)</td>
<td>12 (20)</td>
<td>22 (41)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>18 (3.7)</td>
<td>0 (0)</td>
<td>50 (33)</td>
<td>5 (28)</td>
<td>7 (39)</td>
<td>13 (2)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>PBS</td>
<td>18 (3.7)</td>
<td>14 (78)</td>
<td>54 (78)</td>
<td>11 (2)</td>
<td>2 (11)</td>
<td>2 (11)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Budd-Chiari Syndrome</td>
<td>13 (2.7)</td>
<td>7 (54)</td>
<td>39 (31)</td>
<td>6 (46)</td>
<td>3 (23)</td>
<td>15 (10)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>HBV+HDV</td>
<td>12 (2.5)</td>
<td>4 (33)</td>
<td>53 (47)</td>
<td>7 (58)</td>
<td>3 (25)</td>
<td>2 (17)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>11 (2.2)</td>
<td>6 (55)</td>
<td>57 (43)</td>
<td>7 (64)</td>
<td>3 (27)</td>
<td>2 (17)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>NASH</td>
<td>8 (1.6)</td>
<td>4 (50)</td>
<td>65 (61)</td>
<td>2 (25)</td>
<td>1 (13)</td>
<td>9 (10)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>HBV+HCV</td>
<td>6 (1.2)</td>
<td>2 (33)</td>
<td>57 (50)</td>
<td>2 (33)</td>
<td>1 (77)</td>
<td>10 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>6 (1.2)</td>
<td>4 (67)</td>
<td>48 (67)</td>
<td>2 (33)</td>
<td>1 (17)</td>
<td>12 (2)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>55 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>14 (100)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 3: Cirrhosis and non-cirrhosis rates of HBV and HCV patients.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Cirrhosis (n=197)</th>
<th>Non-Cirrhosis (n=664)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>137</td>
<td>503</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HCV</td>
<td>160</td>
<td>161</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Cirrhosis is one of the most important causes of mortality in our country, as it is all over the world. In the National Burden of Disease-Cost-Effectiveness study conducted in our country in the year 2000, the first 20 diseases leading to mortality at national level have been determined; among the causes of mortality identified in this study, cirrhosis was found to be in the 19th line in the urban regions, and in the 14th line in rural areas. In the USA, cirrhosis disease is the 10th in men among the causes of death, and it is the 12th in women. In cross-sectional study held in our country, it has been reported that a total of 51790 individuals existed with cirrhosis in the year 2004, and 3164 patients died due to cirrhosis.

A single factor causes cirrhosis in some forms of liver disease (HBV, HCV, PBC, primary sclerosing cholangitis, etc.); however in many cases, initiation factors and cofactors may play important roles in the development of cirrhosis. These cofactors include the age of the patient, gender, obesity, alco-
hol consumption, iron intake, and yet unknown genetic factors. In addition, the patient’s age, gender, duration of disease and immunological status may increase the risk of development of cirrhosis. The male gender alone is known to be a cofactor in the development of cirrhosis, and this may be explained by the androgenic negative effects of HBV.

In our study, 230 of the 480 cirrhotic patients were women (48%). When compared with studies conducted in other countries, the female ratio was found to be a little higher. The mean age of the women was 60 ± 13 years. Androgenic effects existing in women after menopause may trigger the development of cirrhosis.

Although frequencies of causes leading to cirrhosis have existed with some minor changes in our country over the years, viral hepatitides are located at the top. In studies performed in the Southeastern Anatolia and Western Anatolia, HBV infection was found to be the most frequent etiologic factor in cirrhosis.

As reported in the studies, HBV is still the first in the etiologies of cirrhosis; being contrary to these results, HCV was found to be the most frequent cause of cirrhosis in our study. In our district, the frequency of HBV is higher than that of the HCV, and in the patients with cirrhosis, a contrary result existed. It may be interpreted that the potent antiviral agents used in the treatment of HBV result in a slower progression to cirrhosis. However, promising novel therapeutic agents started to increase the rate of success in the treatment of HCV. It may be predicted that with the common use of potent treatment modalities, the rate of contribution of HCV to the etiology of cirrhosis would decrease in a gradual manner. Being similar to our results, studies conducted in the United States and Japan report that HCV is the first among the etiologic factors of cirrhosis.

Studies conducted worldwide report that the rates of cryptogenic cirrhosis are between 3% and 10%.[6-8]. This rate had been found to be higher about twenty years ago; however discovery of HCV, and the improvement in the diagnosis of autoimmune, cholestatic and metabolic diseases of the liver, this rate has reduced from 40% to 5%.[17].

In our study, this rate was determined to be 18%. A higher rate of cryptogenic cirrhosis that we found compared with the levels worldwide, may be due to the undiagnosed NASH, autoimmune liver diseases the markers of which are yet unknown, and the occult HBV.

In addition, rare causes like mitochondrialopathies, Familial Mediterranean Fever, Systemic Lupus Erythematosus, abnormalities of apolipoprotein B with low Low-density lipoprotein (LDL) cholesterol, short telomere syndrome, keratin 18 mutations, and glutathione S transferase mutations have also been suggested to be associated with cirrhosis, and they have been considered to be among the possible causes of cryptogenic cirrhosis.[18]. Insufficient diagnostic methods related with these diseases might have also led to the higher rate of cryptogenic cirrhosis that we found.

Additionally, HBV is still a risk factor in the first line among the causes of HCC development. In the studies conducted all around the world, HBV has been reported to cause HCC development by oncogene activation, which is independent of the liver inflammation. A 7- to 30-fold higher HCC risk found in the hepatitis B carriers compared to the healthy individuals which is regardless of the parenchymal damage in liver, support these studies.

As a conclusion, in our district, viral hepatitides and cryptogenic cirrhosis are located in the first lines among the etiologic factors of cirrhosis. It is essential to develop the applications of preventive medicine in the field of viral hepatitides, to widen the screening tests, and to make common the administration of more potent treatment methods. On the other hand, novel tests, and to have these tests commonly applied, are required in order to diagnose the cryptogenic cirrhosis in the hepatitis phase of it, which may possibly be treated. Thus perhaps in the near future, concept of cryptogenic cirrhosis would be completely excluded from the diagnostic list of the physicians.

References


Acknowledgement:
This study was presented at the 24th Annual Conference of the Asian Pacific Association for the Study of the Liver (APASL 2015), March 12-15, 2015, İstanbul, Turkey. We thank the study investigators, coordinators, nurses, patients and their families for their contributions.

Ethical approval
The study was carried out in accordance with the principles of the revised 2013 version of the Declaration of Helsinki of 1975, with the approval numbered 18.05.2015/160 of University of Gaziantep Faculty of Medicine Clinical Research Ethics Committee.

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