The Frequency of Complications and the Etiology of Disease in Patients with Liver Cirrhosis in Erzurum

Erzurum ve Çevresinde Karaciğer Sirozu Hastalarında Hastalığın Etiyolojisi ve Komplikasyonlarının Sıklığı

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Abstract
Objective: This study included 100 patients diagnosed with liver cirrhosis who presented at Ataturk University Faculty of Medicine Gastroenterology clinic and polyclinic.

Materials and Methods: The etiology of liver cirrhosis and the incidence of its complications have been investigated.

Results: The etiological classification of liver cirrhosis in our patients was as follows: 47 hepatitis B virus hepatitis, 11 hepatitis C virus hepatitis, 5 HBV+HDV hepatitis, 4 Budd Chiari syndrome, 2 chronic alcohol abuse, 2 ischemic heart disease, 1 autoimmune hepatitis, 1 sclerosing cholangitis, 1 hydatid cyst. In 26 patients we could not find any etiological condition. These patients were called cryptogenic cirrhosis patients. When we examined the complications of liver cirrhosis, it appeared that there were ascites in 83 patient. In 56 patients, esophageal variceal bleeding occurred. There was spontaneous bacterial peritonitis in 42 patients. Hepatorenal syndrome occurred in 26 patients. Finally, in 3 patients we detected hepatorenal syndrome.

Conclusion: The most common causes in the etiology of liver cirrhosis are viral, especially HBV. Many of the patients were in decompensated phase when diagnosed. We found that there was a close relation between the frequency of complications and mortality in liver cirrhosis.

Key Words: Liver cirrhosis, aetiology, complication

Özet
Amaç: Atatürk Üniversitesi Tıp Fakültesi Gastroenteroloji klinik ve polikliniğine başvuran karaciğer sirozu tanıları 100 hasta incelendi.

Gereç ve Yöntem: Hastalarda karaciğer sirozunun etiyolojisi ve komplikasyonlarının sıklığı araştırıldı.

Bulgarlar: Hastalığın etiyolojisinde hastalarımızın 47’sinde (%47) HBV, 11’inde (%11) HCV, 5’inde (%5) HBV+HDV, 4’ünde (%4) Budd Chiari sendromu, 2’inde (%2) kronik alkol kullanımı, 2’inde (%2) iskemik kalp hastalığı, birinde (%1) otoimmün hepatit,birinde (%1) sklerozan kolanjit, birinde (%1) kisthidatik hastalığı tespit edildi. Yirmi altı hastada (%26) etyolojik sebep bulunamadı, bu hastalar kriptojenik karaciğer sirozu olarak değerlendirildi. Komplikasyonlar arasındadırında 100 hastanın 83’ünde (%83) assit tespit edildi, 56’sında (%56) özefagus varis kanaması gözündi, 42’sinde (%42) spontan bakteriyel peritonit tespit edildi, 26’sında (%26) hepatik ansefalopati tespit edildi. Toplam 3 hastada (%3) hapatorenal sendrom tespit edildi.


Anahtar Kelimeler: Karaciğer sirozu, etyoloji, komplikasyon

Introduction

Hepatic cirrhosis is a progressive disease caused by extensive deterioration of hepatic morphological structures via hepatocellular necrosis, increased connective tissue, hepatic regeneration, nodular formation, and fibrotic tissue [1, 2]. HBV is the main cause of cirrhosis in developing countries. Viral hepatitis is the etiologic factor in 60% of hepatic cirrhosis cases in Turkey [3, 4]. The main complications of hepatic cirrhosis are hepatocellular carcinoma as the result of a lack of hepatocellular functionality, jaundice, coagulation defects and hypoalbuminemia. Variceal bleeding, ascites, ascites infections, hepatorenal syndrome, hepatic encephalopathy, and hepatoportalynary syndrome develop as the results of portal hypertension. The etiology and incidence of disease-related complications in patients diagnosed with hepatic cirrhosis, who presented at the Gastroenterology Clinic and Outpatient Clinic at the Medical School of Ataturk University, were investigated in the current study.
Materials and Methods

The study protocol was approved by the Ethics committee of Ataturk University Faculty of Medicine. In the current study, 100 patients, who were diagnosed with hepatic cirrhosis, and applied to the Gastroenterology clinic and outpatient clinic at the Medical school of Ataturk University between years 2007 and 2010, were investigated. Written informed consent was obtained from patients who participated in this study. When patients were asked the reason for coming to the clinic, they reported complaints such as swelling in the abdomen, jaundice, abdominal pain, swelling in feet and hands, fatigue, black stools, vomiting blood, and disturbance of consciousness. Patients who applied to our clinic with existent complaints were diagnosed with hepatic cirrhosis by physical examination; biochemical, serological and microbiological tests; upper gastrointestinal system endoscopy and ultrasonographic imaging; also, some patients were diagnosed with hepatic cirrhosis by transthoracic echocardiography and hepatic biopsy.

Available tests were considered to define etiological factors of our patients, and all possible causes were investigated. Therefore, our patients were firstly examined for Hepatitis B virus, Hepatitis C Virus, Hepatitis D Virus by using the Enzyme-Linked Immuno Sorbent Assay (ELISA) technique. Autoimmune causes were investigated among our patients, who were negative for the viral etiologies. Antinuclear Antibody, LKM-1, and Anti-smooth muscle antibodies were tested in the serum. Anti-mitocondrial Antibody was studied in patients, who were suspected of cholestatic hepatic disease as the etiology. The patients who were considered to have hepatic cirrhosis due to ischemic causes had transthoracic ECHO, and they were examined for right heart failure and pulmonary hypertension. Our patients who were considered to have alcohol use as the etiological factor, were interviewed in detail. While the patients who were considered to have Budd Chiari syndrome as the disease cause, had Doppler Ultrasonography of the portal vein, patients who were considered to have hydatid cyst as the etiological factor had the serological test of indirect hemagglutination. Hepatic biopsy was performed on 12 of our patients for these reasons, but despite all examinations, etiology was undefined in 26 of our patients.

All of the patients were hospitalized in our clinic ward; follow ups and treatments were conducted; and required tests were performed to define the disease related complications.

Hepatic encephalopathy stage was determined in the patients hospitalized for hepatic encephalopathy, and they were inquired about the number of previous hepatic encephalopathy attacks during their illnesses.

By performing USG, patients hospitalized with the diagnosis of hepatic cirrhosis because of ascites were divided into three groups by the stage of ascites. Paracentesis was performed in the patients with ascites and the serum ascites albumin gradient was measured. Neutrophil levels were determined in the ascites fluid drawn from the patients with ascites, and the values more than 250/mm³ were assessed as peritonitis. Microbiological cultures were prepared with the ascites fluid. Endoscopy was performed on all of our patients by a gastroenterology specialist, and the presence of esophageal varices was investigated. The patients who had previous esophageal variceal bleeding were detected, and the number of variceal bleedings during the disease was determined. Endoscopic band ligation and medical therapy were performed on the patients who were hospitalized because of variceal bleeding. Child Pugh staging was performed on all of our patients.

Results

Of 100 patients included in the study, 58 were males, and 42 were females. The mean age was 55.3±15.9 years with an age range of 16-83 years. Diseases which caused hepatic cirrhosis were HBV in 47 (47%), HCV in 11 (11%), HBV+HDV in 5 (5%), Budd Chiari syndrome in 4 (4%), chronic alcohol use in 2 (2%), ischemic cardiac disease in 2 (2%), autoimmune hepatitis in 1 (1%) 9, sclerosing cholangitis in 1 (1%), and hydatid cyst disease in 1 (1%) patient. No etiological cause was determined in 26 (26%) of our patients, and they were evaluated as cryptogenic. Child staging among patients was Child A in 15 (15%), Child B in 32 (32%), and Child C in 53 (53%) patients during the applications.

While evaluating complication incidence, ascites (n=83, 83%), esophageal variceal bleeding (n= 56, 56%), spontaneous bacterial peritonitis (n=42, 42%), hepatic encephalopathy (n=26, 26%), hepatorenal syndrome (n=3, 3%), esophageal variceal bleeding with spontaneous bacterial peritonitis (n=21, 21%), esophageal variceal bleeding with hepatic encephalopathy (n=11, 11%), spontaneous bacterial peritonitis with hepatic encephalopathy (n=13, 13%), hepatorenal syndrome + hepatic encephalopathy + spontaneous bacterial peritonitis (n=1, 1%), hepatorenal syndrome + hepatic encephalopathy + esophageal variceal bleeding + spontaneous bacterial peritonitis (n=1, 1%), hepatorenal syndrome + hepatic encephalopathy + esophageal variceal bleeding (n=1, 1%) were determined. Esophageal varices were determined in 92 patients (92%); endoscopically defined variceal stages were F1 in 13 patients (13%), F2 in 7 patients (7%), and F3 in 72 patients (72%). Out of 100 patients with hepatic cirrhosis, 56 (56%) were determined to have previous esophageal variceal bleedings: 35 patients (35%) had the bleeding once; 16 patients (16%) had twice, and the remaining 5 patients (5%) had the bleeding three or more times. Among patients with the variceal bleed-
ing, 49 patients (49%) had band ligation, and 5 patients (5%) had endoscopic sclerotherapy. Other patients were followed up by the medical therapy. Of the patients, 17 (17%) had hepatic encephalopathy once; 5 patients had twice; 4 patients had three or more times hepatic encephalopathy. The most common cause of induction of hepatic encephalopathy was esophagus variceal bleeding in 9 patients (9%). The triggering factors were observed, in decreasing frequency, as peritonitis, electrolyte imbalance, constipation, extraperitoneal infections, and diarrhea. Massive ascites was determined in 72 patients (72%); ascites was determined in 5 patients (5%) by performing ascites examination and paracentesis, and in 6 patients by USG examination. Ascites was not observed in 17 patients (17%). Ascites infection was determined in 42 patients (42%). Spontaneous ascites infection was present in all of those patients. Of the patients, 25 had peritonitis attack once during the disease; 15 patients had peritonitis attack twice; two patients had peritonitis attack 3 or more times. Hepatorenal syndrome was determined in 3 patients (3%).

Discussion

The most commonly encountered causes of hepatic cirrhosis are viral hepatitis and alcohol intake. While alcohol intake is the leading cause in Western Europe and North America, viral hepatitis is the leading cause among other moderately developed countries including Turkey [3, 4]. Majority of symptoms and signs encountered in hepatic cirrhosis or complications are non-specific, and their absence does not rule out the cirrhosis [2, 3].

Kim et al. [5] reported from their study conducted on 80 patients with hepatic cirrhosis that the mean age was 59.4 years. Of patients, 58 (72.5%) were males and 22 (27.5%) were females. In the current study, it was determined that 30 patients (37.5%) had hepatic cirrhosis due to alcoholic hepatic disease; 28 patients (35%) had hepatic cirrhosis due chronic HBV; one patient (1.3%) had hepatic cirrhosis due to primary biliary cirrhosis. Seven patients were diagnosed with cryptogenic cirrhosis (5). In our study, 58 patients (58%) were males, and 42 patients (42%) were females. The mean age was 55.3±15.9 years with the age range of 16-83 years. The majority of the patients (n=30) was composed of subjects in the age group of 55-65 years. While the most commonly encountered cause of hepatic cirrhosis was determined as HBV infection, it was determined as alcohol intake in the study of Kim et al. [5].

The role of hepatitis B is very important in chronic hepatitis etiology. Approximately 1/3 of the world population has had HBV infection. It has been estimated that there are around 400 million subjects infected by HBV. It has been considered that approximately 500,000 subjects die annually due to diseases caused by HBV and their complications [6]. In our study, it was determined that viral factors played a role in the etiology of hepatic cirrhosis in more than half of patients (HBV 47%, HCV 11%, HBV+HCV 5%). Chronic hepatitis B infection is the leading etiological factor among chronic hepatic patients in our country.

Early diagnostic and preventive methods directed to the etiology, such as vaccination or protection against hepatitis virus, will cause a significant decrease in the morbidity and mortality. The most important staging in defining the prognosis is Child Pugh staging. In our study, 53 patients (53%) were in the Child C group; 32 patients (32%) were in Child B, and 15 patients (15%) were in Child A groups. This finding was the sign that more than half of the patients applied to a clinic in the advanced stage [6]. While it was reported in previous studies that HBV had a place of approximately 20% in the etiology of hepatic cirrhosis, the rate was observed to have increased to 80-90% in the recent years, because of development and common use of the Elisa method [7].

In a study conducted in the Diyarbakir region, 75 out of 100 patients (75%) with hepatic cirrhosis were positive for HBV alone or for HBV+HCV. HBV was determined alone in 40 of those cases; HBV+HDV positivity was determined in 27 patients (27%), and HCV+HBV+HDV positivity was determined in 5 patients (5%). Moreover, HCV positivity was observed alone in 3 cases. Our study was similar to the study conducted in the Diyarbakir region in etiological causes [8].

Otu reported [9] that hepatitis B virus was responsible for 90% of the etiology in hepatic cirrhosis patients in Nigeria, where hepatitis viruses were very commonly encountered. Gandhi et al. [10] reported on a study conducted in India that hepatitis B virus was responsible for the etiology of hepatic cirrhosis patients at 81.8%. In our study, the most common etiological cause of hepatic cirrhosis was determined as HBV. Our study was similar to those previous studies.

In European countries, HCV was reported to the most common cause of hepatic cirrhosis among hepatitis viruses, because HBV incidence was low. For example Amitrano et al. [11] reported in their study from Italy that HCV caused hepatic cirrhosis at an incidence of 45%. When etiological causes of our patients were investigated, HBV and HCV were observed at 47% and 11%, respectively. The most common cause of hepatic cirrhosis was defined as HBV in our region [11]. Studies conducted in European countries showed differences from our study in the incidence of etiological causes. HBV related hepatic cirrhosis has rarely been encountered in European countries compared to our country.

It was observed that alcohol consumption had an important place in the etiology of hepatic cirrhosis in European countries. However, the main cause of hepatic cirrhosis in oriental countries is HBV. Although HBV actually has frequently been observed in Asia, the cause of two-thirds of Japanese...
patients with hepatic cirrhosis was HCV. Genetic disorders and exposure to aflatoxin and parasitic infections are the major etiological causes for hepatic cirrhosis in Australia and Southeast Asia, respectively [12].

Complications such as hepatic encephalopathy, ascites, and esophageal variceal bleeding are the causes of morbidity and mortality to a greater extent [13]. In a Japanese cohort study conducted by Morivaki et al. [12] it was reported that the annual rate of hepatic encephalopathy development among complications was 8% in cases with decompensated cirrhosis. The major cause of hepatic encephalopathy attack was massive gastrointestinal bleeding from esophageal varices or acute gastric mucosal lesions. Moreover, conditions such as constipation, diarrhea, and inappropriate diuretic intake are among the other causes of chronically recurrent hepatic encephalopathy. A stimulating factor has not been found in approximately 30-40% of cases with hepatic encephalopathy. In our study, 74% of our patients did not experience any hepatic encephalopathy, whereas only 26% experienced hepatic encephalopathy. When the causes of hepatic encephalopathy in our cases were investigated, the leading cause was esophageal variceal bleeding (n=9), and the other causes were peritonitis, electrolyte imbalance, constipation, extra-peritoneal infections, and diarrhea, in decreasing order. Our study showed similarity to the study conducted by Morivaki et al [12]. Hepatic encephalopathy was reported as 8% among patients in studies from the Far East. Hepatic encephalopathy is one of most important clinical pictures in decompensated hepatic cirrhosis. The majority of studies related to decompensated hepatic cirrhosis originated in western countries. In those studies, it was reported that hepatic encephalopathy was 8% and ascites was 7% in hepatic cirrhosis patients without previous history of decomposition. Hepatic encephalopathy was determined in 26% and ascites was determined in 81% (n=81) of the patients in our study. A difference has been observed between etiological causes and complication development in the studies conducted among Eastern and Western countries [12].

Esophageal varices were encountered in 30% of compensated cirrhosis patients, as opposed to 60% in decompensated cirrhosis patients; each bleeding has a mortality risk of 20%. Recurrent bleeding risk in 1 year is 70% in untreated cases [13]. Of the patients, 56 had esophageal bleeding previously; 35 patients had bleeding once, and 16 had it twice. The remaining five patients had bleeding three or more times. Band ligation was performed in 49 patients with esophageal variceal bleeding, and endoscopic sclerotherapy was performed in five patients with bleeding. Other patients who had esophageal variceal bleeding were followed up medically. In our study, it was observed that 28 patients with esophagus variceal bleeding did not take propranolol before the bleeding, whereas 19 patients took it at inadequate doses. Thirteen of our patients (13%) died because of bleeding.

Schepeke et al. [14] conducted a study on 152 patients with cirrhosis; they performed band ligation on 75 of them, and they gave non-selective beta blockers to 77 of them. They indicated that prophylactic endoscopic band ligation procedure could be used in patients who could not tolerate beta blockers, and there was no difference in preventing recurrent bleeding. In our study, 72 (72%) of our patients used prophylactic propranolol.

In their study, Garcia et al. [15] determined that gastrointestinal varices were present in 50% of patients with hepatic cirrhosis. It was reported that esophageal variceal bleeding was observed in approximately 15% of patients in the first year. In the current study, esophageal varices were determined in 92 patients (92%). Esophageal variceal bleeding was observed in 56 patients (56%) in our study. Frequency of esophageal variceal bleeding was more common in our study compared to that study.

Spontaneous bacterial peritonitis was reported in approximately 30% of patients in the literature. It was diagnosed with PNL above 250/mm² in the paracentesis fluid [16]. In the study conducted in 1971, spontaneous bacterial peritonitis prevalence was determined as 5-10% in patients with cirrhotic ascites. In later conducted studies patients were followed up by using improved culture techniques, and spontaneous bacterial peritonitis prevalence was reported as 10-30% [17].

In a study conducted in the Northern India by Puri AS et al. [18] it was determined that spontaneous bacterial peritonitis was present in 30% of patients, who were followed up in the hospital for hepatic cirrhosis. In our study, spontaneous bacterial peritonitis was determined in 42 patients (42%) and IV cefotaxime and ciprofloxacin treatments were used. Our study showed similarity to the study conducted in the Northern India region in complication frequency.

In the study conducted by Fasolato et al. [19] 309 patients with hepatic cirrhosis were investigated. Ascites was determined in 233 patients (75.4%). Spontaneous bacterial peritonitis was determined in 104 cases (44.6%). In this present study, spontaneous bacterial peritonitis was observed concomitantly with hepatorenal syndrome in 35 patients (33.6%). In our study, ascites was determined in 83 patients (83%) with hepatic cirrhosis, and spontaneous bacterial peritonitis was determined in 42 patients (42%). Our study was similar to that study in the complication frequency.

Agelly et al. [20] observed in their study conducted on 29 patients with cirrhosis that prophylactic antibiotic use in recurrent spontaneous bacterial peritonitis attacks decreased the number of attacks. In our study, it was observed that spontaneous bacterial peritonitis was developed in 42 of our patients with hepatic cirrhosis. Our 25 patients had peritonitis...
once during the disease and 15 of our patients had the attack twice whereas two patients had it three or more times during the course of the disease.

Kim et al. [5] determined that spontaneous bacterial peritonitis was observed concomitantly with renal dysfunction in 29 (36%) out of 80 patients with hepatic cirrhosis. Among our patients, spontaneous bacterial peritonitis was observed with hepaticorenal syndrome in only one patient. There was no difference in complication frequency between our study and the study of Kim et al. [5] Hepatorenal syndrome was observed less frequently in our study.

Fallo et al. [21] reported that mortality was 100% in 252 patients with hepatic cirrhosis who developed hepatorenal syndrome. In our study, there were three patients (3%) with hepatorenal syndrome, and all died because of it. Our study showed similarity with the study conducted by Fallo et al. [21].

One or more of these causes might be observed in the 70-100% of patients who developed hepatorenal syndrome [22]. Hepatorenal syndrome was encountered in 3 of our patients; the triggering causes of hepatorenal syndrome development were spontaneous bacterial peritonitis in 1 patient and esophageal variceal bleeding in two patients.

Etiological causes and complication frequency of included patients were similar to many studies conducted nationally and internationally, and they were consistent with the literature.

In conclusion, hepatic cirrhosis is a disease with high mortality. From a public health perspective, training is required. Hepatitis viruses are still the most common cause in the etiology of hepatic cirrhosis. The main causes of the morbidity and mortality in hepatic cirrhosis were disease related complications.

**Ethics Committee Approval:** Ethics committee approval was received for this study (14.01.2011).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.


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