Dicle Tıp Dergisi /
Dicle Medical Journal

2015; 42 (4): 416-421
doi: 10.5798/diclemedj.0921.2015.04.0601

ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Hepatitis B virus is still the most common etiologic factor of liver cirrhosis: Results from a single center in Turkey

Hepatit B virüsü karaciğer sirozunun halen en yaygın etyolojik faktörüdür: Türkiye'de tek merkezden sonuçlar

Sebahat Başyigit[1], Zeliha Asiltürk[2], Ferdane Sapmaz[3], Ayşe Kefeli[4], Abdullah Özgür Yeniova[5], Metin Uzman[3], Yaşar Nazligul[3]

ABSTRACT

Objective: It is important to examine the epidemiology of liver cirrhosis (LC) because of it is a preventable disease. In this single-center study, we aimed to determine the epidemiological characteristics and etiology of LC in Central Anatolian region of Turkey.

Methods: We reviewed data of patients with liver cirrhosis who presented to outpatient and inpatient clinics of our medical center between January 1, 2011 and September 31, 2014

Results: Overall, 135 patients were included to the study: 91 men (67.4%) and 44 women (33%) with a mean age of 63±14,3 years (range: 15–87years). The primary causes of cirrhosis were chronic hepatitis B (CHB) (n: 52, 38.5%) and cryptogenic cirrhosis (n: 33, 24.4%). CHB was the main etiology of cirrhosis in men (49.5%) and cryptogenic LC was predominant in women (40.9%). Patients with alcoholic cirrhosis were solely male. Percentage of patients with autoimmune hepatitis was significantly higher among women (70%). The percentage of patients with HBV was similar between patients aged<50 and >50 years (31.6% and 39.7%, respectively), but percentage of patients with hepatitis C virus was lower (5.3%) in patients aged<50 years when compared to those aged>50 years (14.7%). There was no cirrhotic patients under 50 years of age due to a genetic disorder

Conclusion: Despite national vaccination program, effective treatment regimens and intensive screening methods against hepatitis B virus, it remains to be the most common cause of LC in our country.

Key words: Viral hepatitis, alcohol induced liver disease, autoimmune hepatitis, cryptogenic liver cirrhosis, non-alcoholic fatty liver disease

ÖZET

Amaç: Karaciğer sirozu sebepleri yönünden önlenebilir bir hastalık olduğu için epidemiyolojisinin araştırılması önemlidir. Biz bu tek merkezli çalışmada, Türkiye'nin Orta Anadolu bölgesinde, karaciğer sirozunun etyolojik nedenlerini ve epidemiyolojik özelliklerini belirlemeyi amaçladık.

Yöntemler: 1 Ocak 2011 ve 31 Eylül 2014 tarihleri arasında sağlık merkezimizdeki yataklı ve ayaktan kliniklere başvurmuş olan karaciğer sirozu tanılı hastalar kaydedildi.

Bulgular: Toplam 135 hasta çalışmaya dahil edildi: ortalama yaşı 63±14.3 (minimum:15 ve maksimum:87 yaş) olan 91 erkek hasta (%67,4) ve 44 kadın hasta (%33). Sirozun temel nedenleri: Kronik hepatit B (KHB), (n:52, %38,5) ve kriptojenik, (n:33, %24,4) idi. Sirozun en sık nedeni erkeklerde KHB (%49,5) ve kadınlarda kriptojenik karaciğer sirozuydu (%40,9). Alkolik sirozu olan hastaların tamamı erkekti. Otoimmün hepatiti olan hastaların oranı kadınlarda anlamlı olarak yüksekti (%70). 50 yaş altındaki ve üstündeki sirotik hastalar arasında KHB'li hastaların oranı benzerdi (sırasıyla;%31,6 ve %39,7), ancak 50 yaş altındakilerde hepatit C virüsü olan hastaların oranı, 50 yaş üstündekilere göre anlamlı olarak daha azdı (%5,3 ve %14,7). 50 yaş altında genetik bozukluğa bağlı sirotik hasta yoktu.

Sonuç: Hepatit B virüsüne karşı Ulusal aşılama programı, etkin tedavi önlemleri ve artırılmış tarama tetkiklerine rağmen, KHB halen ülkemizde en sık siroz nedenidir.

Anahtar Kelimeler: Viral hepatit, alkole bağlı karaciğer hastalığı, otoimmun hepatit, kriptojenik karaciğer sirozu, non-alkolik yağlı karaciğer hastalığı

[1] Artvin State Hospital, Department of Gastroenterology, Artvin, Turkey
[2] Keçioren Research and Training Hospital, Department of Internal Medicine, Ankara, Turkey
[3] Keçioren Research and Training Hospital, Department of Gastroenterology, Ankara, Turkey
[4] Siirt State Hospital, Department of Gastroenterology, Siirt, Turkey
[5] Gaziosmanpaşa University, Faculty of Medicine, Department of Gastroenterology, Tokat, Turkey

***Yazışma Adresi /Correspondence:** Sebahat Başyiğit,*
Artvin State Hospital, Department of Gastroenterology, Artvin, Turkey Email: sbuyuktemiz@yahoo.com

Geliş Tarihi / Received: 10.11.2015, Kabul Tarihi / Accepted: 06.12.2015

INTRODUCTION

Liver cirrhosis (LC) is a common health problem worldwide, which is characterized by irreversible damage of the liver parenchyma. It has life-threatening complications including upper gastrointestinal bleeding, hepatic encephalopathy and hepatocellular carcinoma at the decompensated stage. The epidemiological distribution of LC etiology varies geographically and remains to be poorly described. Because cirrhosis and its complications may be preventable, it is important to document its epidemiology [1].

In Western countries, hepatitis C virus (HCV) and alcohol have been reported to be the most common causes, whereas hepatitis B virus (HBV)-related LC is predominant in most Asian-Pacific and African countries [1-3]. Recently, the epidemiology and etiology have changed dramatically because of socioeconomic development and hepatitis vaccination; however, the available, comprehensive information is limited worldwide.

In 2007, viral hepatitis was reported to be the etiologic factor in 60% of LC cases in Turkey [4]. Turkey is located geopolitically important region between Europe and Asia. As Turkey is achieving rapid advances in socioeconomic status and one of the major centers of tourism, Turkey is vulnerable to great changes in the epidemiology of the disease over time. However, epidemiologic data of LC from Turkey is scarce. There is need for a novel epidemiological mapping of LC in Turkey. In this single-center study, we aimed to investigate whether there is a change in the etiology and epidemiology of liver cirrhosis over time in Central Anatolia.

METHODS

We reviewed the medical records of all patients admitted between January 1, 2011 and September 30, 2014 by using electronic database of our facility. Patients who were diagnosed with LC were included to the analysis. The search included any diagnostic or therapeutic codes for LC, esophageal varices, or portal hypertension as discharge diagnosis. To minimize the potential of missing cases with underlying LC but lacking the above diagnostic codes, we performed a second search in the database for non-malignant ascites, hepatic encephalopathy and hepatorenal syndrome. A final diagnosis of LC and etiology were decided according to discharge diagnosis; if no apparent etiology was suggested, the etiological diagnosis was established based on the criteria below. Moreover, patients who had no clinical features of chronic liver disease but exhibited a positive pathological diagnosis or did not undergo laboratory tests for evaluation of liver function were excluded. In patients with multiple admissions during study period, we only collected the first record where the LC diagnosis was established. In each patient, we collected clinical information including age, gender and etiology of cirrhosis.

Criteria for the diagnosis of liver cirrhosis

The diagnosis of LC was made according to the diagnosis of LC or complication of LC in the medical records. Recurrent records were deleted by controlling patient's national ID. Prevalance of patients who had diagnosis of esophageal varices, ascites, hepatorenal syndrome, hepatocellular carcinoma, or hepatic encephalopathy were also recorded.

Definition of etiologic factors

The diagnosis of viral hepatitis was based on positive serology for hepatitis (positive hepatitis B surface antigen for more than six months or positive HCV-RNA). Alcoholic liver disease was diagnosed based on history of significant alcohol intake (more than 21 units of alcohol per week for men, and 14 units per week for women) in the absence of other significant risk factors for chronic liver disease as the main etiology. Wilson's disease, hereditary hemochromatosis, other metabolic deposition diseases (amyloidosis, glycogen storage disease, etc.) diagnosed by liver histology or laboratory investigations were defined as genetic disorders. Autoimmune etiologies include autoimmune hepatitis (AIH), primary biliary cirrhosis (PBS) and primary sclerosing cholangitis (PSC) which were diagnosed based on serological, histological or imaging techniques. Cryptogenic cirrhosis was diagnosed only after an extensive evaluation excluding recognizable etiologies. Secondary biliary cirrhosis, drug-induced liver failure, non-alcoholic liver disease and vascular causes were defined as other causes.

Statistical Analysis

The data were analyzed by using SPSS® (IBM, version 16.0, Chicago, Illinois, USA). Categorical variables were expressed as number and percentage and compared by using Chi-square test. Continuous variables were expressed as mean ± SD. A two-sided p value <0.05 was considered to be statistically significant.

RESULTS

During study period of years from 2011 to 2014, 135 patients diagnosed as cirrhosis were identified who admitted to our medical center. Table 1 shows demographic and clinical features of study population. Majority of patients were male (n: 91, 67.4%). The female: male ratio was 1:2. The mean age of study population was 63.0 ± 14.3 years (range: 15–87years). The mean age was 61.5±15.6 years in men and 66.2±15.4 years in women. There was no significant difference in mean age between men and women (p: 0.078). Figure 1 shows age distribution of patients (Figure 1).

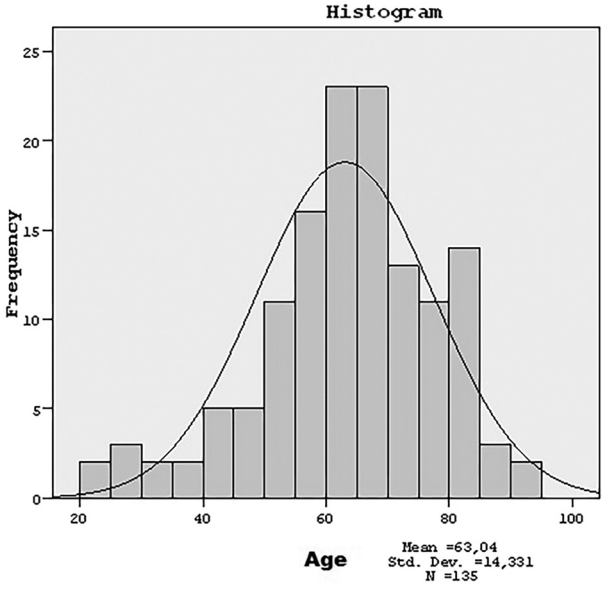

Figure 1. Age distribution of study patients

The major causes of cirrhosis were HBV (n: 52, 38.5%) and cryptogenic (n: 33, 24.4%); followed by HCV in 13.3%; alcohol intake in 10.4%, autoimmune causes in 7.4%; genetic disorders in 1.5% (of these patient, one had Wilson's disease and the other had hereditary hemochromatosis); and 4.4% had other reasons (Table 1). Complication rates were also presented in table 1.

Table 1. Demographic and clinical characteristics of the patients

Parameters	n (%)
Mean age (years)	63 ± 14.3
>50 years	113 (83.7)
≤50 years	22 (16.3)
Gender	
Female	44 (32.6)
Male	91 (67.4)
Etiology	
HBV	52 (38.5)
HCV	18 (13.3)
Alcohol	14 (10.4)
Cryptogenic	33 (224.4)
Genetic	2 (1.5)
Autoimmune	10 (7.4)
Others	18 (13.3)
Complications	
Esophageal varices bleeding	37 (27.4)
Hepatic encephalopathy	23 (17)
Spontan bacterial peritonitis	42 (31.1)
Ascites	54 (40)
Hepatopulmonary syndrome	2 (2)
HCC	7 (5)

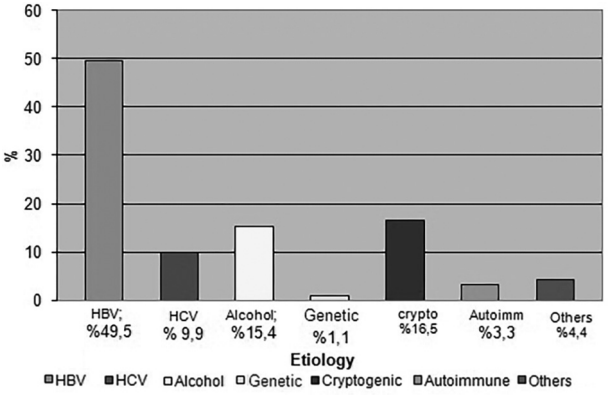

Figure 2. Distribution of Liver Cirrhosis Etiology in men

Table 2 shows distribution of etiological causes by gender. HBV was the main etiologic factor in cirrhotic men (49.5%) and cryptogenic cirrhosis was the predominant etiology in cirrhotic women (40.9%). Patients with alcoholic cirrhosis were solely male. Percentage of patients with autoimmune etiologies was higher in women (70%). There

was significant difference in etiology between men and women (p<0.001) (Table 2).

Table 3 shows distribution of etiological causes by age. HBV was primary reason in patients regardless of age. The percentage of patients with HCV was lower in patients aged<50 years compared to those aged>50 years (5.3% vs. 14.7%), indicating no significant difference. All patients with genetic disorders were younger than 50 years old (p= 0.012) (Table 3).

Table 2. Etiologic distribution based on gender in patients with liver cirrhosis

Etiology	Male (n=91) n (%)	Female (n=44) n (%)	p value
Hepatitis B	45 (86.5)	7 (13.5)	<0.001
Hepatitis C	9 (50.0)	9 (50.0)	0.08
Alcohol	14 (100)	0	0.003
Cryptogenic	15 (45.5)	18 (54.5)	0.002
Genetic Disorders	1 (50)	1 (50)	0.547
Autoimmune	3 (30.0)	7 (70.0)	0.014
Others	8 (44.4)	10 (55.6)	0.633

Table 3. Distribution of etiological causes by age

Etiology	≤50 years (n=22) n (%)	>50 years (n=113) n (%)	p value
Hepatitis B	7 (13.5)	45 (86.5)	0.324
Hepatitis C	1 (5.6)	17 (94.4)	0.163
Alcohol	3 (21.4)	11 (78.6)	0.407
Cryptogenic	4 (12.1)	29 (87.9)	0.327
Genetic Disorders	2 (100)	0	**0.026**
Autoimmune	2 (20)	8 (80)	0.509
Others	3 (50)	3 (50)	0.055

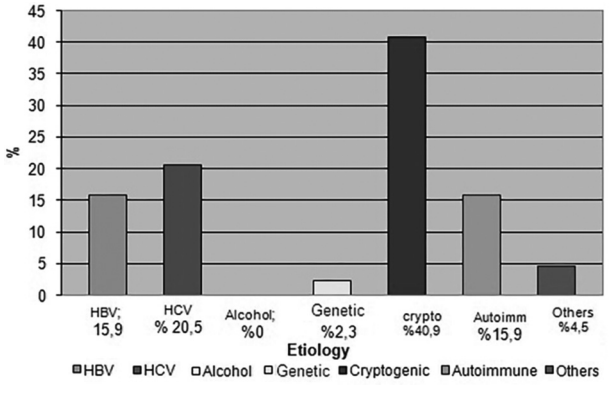

Figure 3. Distribution of Liver Cirrhosis Etiology in Women

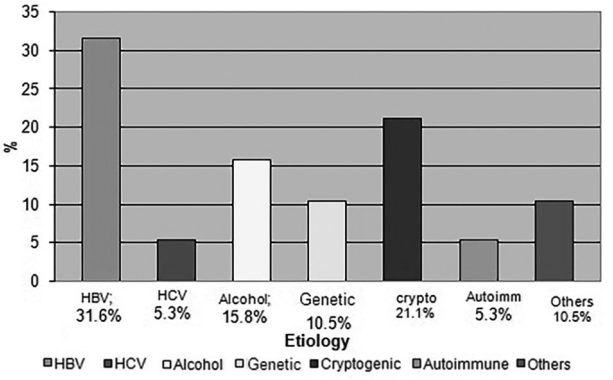

Figure 4. Distribution of Etiology of Cirrhosis under 50 years old

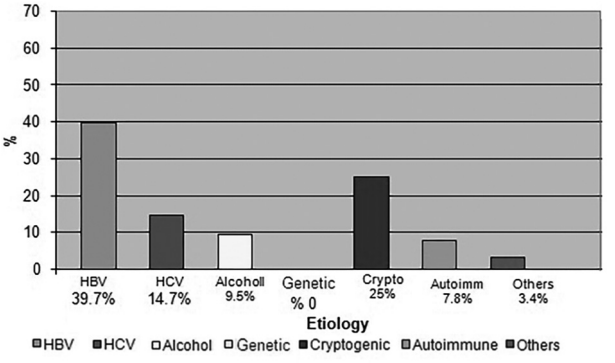

Figure 5. Distribution of Etiology of Cirrhosis over 50 years old

DISCUSSION

In this study, we showed that HBV remains to be the primary cause of LC in our center. Approximately one-third of the world population had HBV infection [6]. According to a study in 2010 by TURKHEP, carrier rate for hepatitis B virus was 4% in Turkey [7], suggesting that there was an estimated 3 million HBV carriers, 1 million of whom developed chronic hepatitis B in Turkey. HBV plays very important role in chronic hepatitis etiology and is a major cause of LC in developing countries. In a study in 1994 from Turkey, it was shown that 75% of cases with LC were positive for HBV in Diyarbakır region [8] and HBV was identified in 47% of cirrhotic patients in another study conducted between 2007 and 2010 in Erzurum region [9]. In consistent with the previous results, we found that more than one-third of patients with LC had HBV (38.5%) as the etio-

logical factor. Although blood transfusion services is using ELISA techniques for detection of HBsAg; marked hygienic measures are implemented; positive developments were achieved in public health area; antiviral treatments have been introduced; and HBV vaccination has been endorsed by the Ministry of Health for all newborns in Turkey since 1998, the burden of HBV is still high in our region. However, it is anticipated that the HBV incidence will decline as the rate of immunized individuals increases.

HCV and alcohol consumption are the major causes of LC in Western countries. However, results of two studies from our country showed that HCV was responsible in approximately 5% of cirrhotic cases in Diyarbakır in 1994 and in 11% of cases in Erzurum between 2007 and 2010 [8, 9]. Our results indicating 13.3% of cases had HCV confirm the previous results. Chronic alcohol consumption was found in 10.7% of cases, all which were male. Studies from Eastern Turkey have showed lesser ratio of alcoholic etiology as low as 2%, reflecting the important role of social factors.

Cryptogenic etiology was higher than expected in our study. It was the second leading cause of the LC. The reason for being the second most often etiology of cryptogenic cirrhosis is thought to be due to the the high prevalence of underdiagnosed cases of non-alcoholic steatohepatitis (NASH). Majority of cases with cryptogenic cirrhosis might be end-stage NASH. In Western countries, NASH becomes increasingly prevalent while prevalence of viral hepatitis displays a decrease in recent years [10]. This increase may be related to the increased awareness and diagnosis of the disease. Our results emphasize the need for more comprehensive evaluation including liver biopsy for patients with NASH. Importantly, it is a preventable disease with simple alterations in life-style. Our patients with cryptogenic etiology were predominantly female. Earlier impressions that NASH has female preponderance condition are dispelled in recent years; in fact, it appears to be more prevalent in men. Since metabolic syndrome (MS) is highly related with NASH [11] and MS prevalence is higher in women than men in Turkey [12], our results may be affected by this distribution.

PBC, AIH and PSC are chronic liver diseases that likely have an autoimmune basis in their pathogenesis. Unfortunately, considerably less is known about the prevalence of autoimmune diseases in patients with LC. There is a marked female predominance in AIH and PBS but PSC is more common in men [13]. In our study, patients with autoimmune etiologies comprised 7.4% of cases and were predominantly female.

LC due to the genetic disorders such as Wilson's disease or hereditary hemochromatosis has low prevalence worldwide. Liver involvement by genetic disorders is usually manifested in late childhood and adolescent period, and progressively produces LC. In general, as the age of the patient is younger at symptom onset, the degree of liver involvement will be the greater over time. The only effective treatment is liver transplantation after the LC became evident. This diseases also preventable by chelation therapies, but an interruption to therapy or inadequate treatment can lead to fatalities within 9 months to 3 years [14,15]. As expected, metabolic causes were found in patients younger than 50 years of age in our study. Genetic disorders were found in 1.5% of patients with LC.

Factors independently associated with LC include age and male gender [16]. In our study we found that mean age of patient was 63±14.3 years and male: female ratio was 2 in accordance with the previous studies.

In conclusion, prevalence of LC increases with age and shows male predominance. Because national vaccination program against HBV was started in 1998, it is the most common cause in adult population in our country. Our results about the etiological distribution of LC were in consistent with previous data.

REFERENCES

1. Grant BF, Dawson DA, Stinson FS, et al. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991–1992 and 2001–2002. Drug Alcohol Depend 2004;74:223–234.
2. Di Bisceglie AM. Natural history of hepatitis C: its impact on clinical management. Hepatology 2000;31:1014–1018.
3. Merican I, Guan R, Amarapuka D, et al. Chronic hepatitis B virus infection in Asian countries. J Gastroenterol Hepatol 2000;15:1356–1361.
4. Ökten A. Karaciğer sirozu. In: Büyüköztürk K, Atamer T, Dilmener M, eds. İç Hastalıkları cilt-1, 1st edn. Ankara: Nobel Tıp Kitabevi, 2007:1077-1088.

5. Michitaka K, Nishiguchi S, Aoyagi Y, et al. Etiology of liver cirrhosis in Japan: a nationwide survey. J Gastroenterol 2010;45:86-94.

6. Değirmencioğlu ZA. Hepatit B'ye bağlı siroz hastalarında Child Pugh evrelemesine göre HBV DNA düzeylerinin karşılaştırılması. İç hastalıkları ihtisas tezi. İnönü Üniversitesi Tıp Fakültesi, Malatya, 2009.

7. Tozun N, Ozdogan OC, Cakaloglu Y, et al. A nationwide prevalence study and risk factors for Hepatitis A, B, C and D infections in Turkey. Turkey Liver Research Association National Hepatitis Often Study (TURKHEP 2010). Hepatology 2010;52:697.

8. Ayyıldız MO. Yöremizde karaciğer sirozunda HBV, HCV ve HDV'nin rolü. İç Hastalıkları ihtisas tezi Dicle Üniversitesi Tıp Fakültesi, Diyarbakır, 1994.

9. Topdagi O, Okcu N, Bilen N. The Frequency of Complications and the Etiology of Disease in Patients with Liver Cirrhosis in Erzurum. The Eurasian Journal of Medicine 2014;46:110-114.

10. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 2006;43:99-112.

11. Demir ME, Aydoğan T, Pamukcu M, et al. Ultrasound evaluation of metabolic syndrome patients with hepatosteatosis J Clin Exp Invest 2013;4:153-158.

12. Temizhan A, Korkmaz A. Metabolik Sendrom Tanısı ve Epidemiyolojisi. Turkiye Klinikleri Journal of Endocrinology Special Topics 2011;4:1-6.

13. Feld JJ, Heathcote EJ. Epidemiology of autoimmune liver disease. J Gastroenterol Hepatol 2003;18:1118-1128.

14. Das SK, Ray K. Wilson's disease: an update. Nature Clinical Practice Neurology 2006;2:482-493.

15. Tuğ E, Balaban YH. Wilson Disease: Case Report. Dicle Med J 2007;34:57-60.

16. Poynard T, Lebray P, Ingiliz P, et al. Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest) BMC Gastroenterol 2010;10:40-53.