ORIGINAL ARTICLE

ETIOLOGICAL SPECTRUM OF CIRRHOSIS IN ANAND DISTRICT, GUJARAT, INDIA

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ABSTRACT

Introduction: Alcohol is considered to be a major etiological factor in western world, whereas viral etiology is considered to be predominant cause of cirrhosis in Indian subcontinent. Alcohol consumption and subsequent cirrhosis is increasingly seen in countries such as Japan and India. Early diagnosis and specific treatment for etiology can reverse the cirrhosis. Thus, we planned this study to define etiology for the development of cirrhosis.

Methodology: All the consecutive patients with cirrhosis in last 4 years (February, 2012 to November, 2016) were analyzed for etiology. They underwent for the following investigations: liver function tests, complete blood count, alcohol and drug history, HBsAg, total anti HBc, anti HCV, Alpha Feto Protein, Ferritin, Ceruloplasmin, eye check up for KF ring, α1-antitrypsin, autoimmune hepatitis profile, sonography and doppler of abdomen, 2-D echocardiography, endoscopy and liver biopsy.

Results: A total of 304 cirrhotic patients (217 males, 87 female) were included and etiologies of cirrhosis were as follows [n (%)]:Alcohol in 105 (34.53%), Non Alcoholic Fatty Liver Disease (NAFLD) in 66 (21.71%), Cryptogenic-probable NAFLD in 50 (16.44%), Hepatitis B cirrhosis (HBV) in 35 (11.53%), Hepatitis C cirrhosis (HCV) in 16 (5.26%), Cryptogenic Cirrhosis in 16 (5.26%), Autoimmune liver disease in 7 (2.30%), Metabolic causes in 6 (2%) and Budd-chiari syndrome in 3 (0.98%).

Conclusions: Alcohol remained the most common etiology of cirrhosis most commonly in males. NAFLD is also a major factor for cirrhosis, followed by HBV and HCV. Metabolic, autoimmune and vascular etiologies were seen in few patients. Most etiologies have peculiar age distribution.

Key words: Cirrhosis, NAFLD, HBV

INTRODUCTION

Cirrhosis has become a common disease due to heavy intake of alcohol in most countries, high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections; and new epidemic of non-alcoholic fatty liver disease (NAFLD).[1]There is a trend towards increase in prevalence of cirrhosis and subsequent morbidity and mortality worldwide.[1,2]

According to recent WHO estimate, end-stage liver disease is responsible for one in forty deaths (2.5%) throughout the World.[3] As a cause of mortality, cirrhosis ranks fifth most common in UK and ninth most common in USA.[1,4,5] A recent Scotland data suggests liver-related mortality has increased by double in males and by half in females.[6] Increase in cirrhosis is getting translated in increasing prevalence of HCC worldwide, as 2-6% of all cirrhotics will develop HCC every year.[7,8,21] HCC is responsible for 0.5 million deaths every year. Eventually increased prevalence of cirrhosis will lead to increased burden on liver transplantation program, as liver transplantation is the only available treatment that improves survival and quality of life.

Alcohol is considered to be a major etiological factor for cirrhosis in western world and there is a rising prevalence of alcoholism in young, women and affluent class.[1] Alcohol accounts for 80% of all liver cirrhosis cases seen in district general hospitals in the UK. Alcohol consumption and subsequent cirrhosis is increasingly seen in countries such as Japan and India which traditionally had a low prevalence of the disease.[9, 25] HCV is steadily on rise in Europe, USA, Egypt and Japan. HBV is highly prevalent in Asia and sub-Saharan Africa.[1] With globalization, cheap air travel and immigration, these viral infections are spreading in variable frequency throughout the World.[1] NAFLD has become commoner worldwide than before because of worldwide epidemic of obesity and diabetes.[1] Autoimmune, metabolic, toxic, vascular and genetic disease represent minority of cases

of cirrhosis. Of all chronic liver disease, 5-30% remains cryptogenic despite multiple investigations, Burnt-out NAFLD, burnt-out autoimmune liver disease, occult viral infections and occult alcoholism may be responsible for these cases.

Predicted burden of cirrhosis in India {general population (recent estimate: 1200 million)} is huge and varies according to different etiologies: Alcohol (prevalence 5% and % expected to be cirrhotic 10%) 7.5 million, HBV (prevalence 3% and % expected to be cirrhotic 15%) 7.5 million, HCV (prevalence 1% and % expected to be cirrhotic 10%) 2.2 million and NAFLD (prevalence 10% and % expected to be cirrhotic 5%) 7.5 million persons. Exact distribution of etiologies among cirrhotics is not well studied. It is commonly perceived that viral etiology especially HBV is predominant cause of cirrhosis in Indian subcontinent. Data regarding this matter is sparse. According to WHO estimate, in India per capita alcohol consumption is around 2 liters of alcohol and prevalence of alcoholism is 15-30% in males and 4-10% in females.[9] Previous estimates have shown alcohol to be caused of cirrhosis in 16% in biopsy proven cases.[9]

Early diagnosis and specific treatment for etiology can reverse the cirrhosis and thus prognosis and survival of these patients can be improved.[11, 12] Hence the aim of this study was to find out various etiological factors for the development of liver cirrhosis.

METHODOLOGY

This prospective observational study was carried out at Jivandeep Hospital and Shri A. N. Patel Post Graduate Institute, Anand, Gujarat, India from February, 2012 to October, 2016. 304 consecutive patients of cirrhosis living in Anand city or nearby villages attending hospital were selected randomly for the study. All those patients who were not confirmed to be cirrhotic, excluded from this study. All the patients were carefully examined to determine the etiology of the disease and related complication(s). Cirrhosis was diagnosed on the basis of presence of history of decompensation, stigmata of the chronic liver disease, portal hypertension on imaging, esophageal varices on endoscopy and/or cirrhosis on histology.[10] Data were recorded on a proforma specially designed for this purpose.

All the patients of cirrhosis underwent for the following investigations to define etiology: CBC (includes Hb, platelet count and TC), liver function tests (includes Bilirubin, SGPT, SGOT, SAP, GGTP, Albumin, Globulin and PT), alcohol and drug history, HBsAg, total anti HBc, anti HCV, Alpha Feto Protein, Ferritin, Ceruloplasmin, eye check up for KF ring, α1-antitrypsin, autoimmune hepatitis profile (gamma globulin, IgG, ANA, ASMA, AMA, anti LKM-I, SLA/ LP, LC1, P-ANCA), sonography and doppler of abdomen, 2-D echocardiography, endoscopy and liver biopsy (as and when needed). This study was approved by the Institutional Human Research Ethics Committee. The study patients were informed about the objective of the study. An informed consent was taken from all cirrhotic patients.

Statistical analysis: Data were statistically analysed using the SPSS statistical software (version 20 for windows). Values of parameters were expressed as Mean ± S.D. "*p*" values less than 0.05 (two-sided) were considered to indicate statistically significant result.

RESULTS

A total of 304 cirrhotic patients (mean age = 50 ± 16 years) were included in the study. Among them, 217 were males (71.38%) and 87 were female (28.62%).

Etiology of cirrhosis: Etiologies of cirrhosis were as follows: Alcohol in 105 (34.53%), NAFLD in 66 (21.71%), Cryptogenic (probable NAFLD) in 50 (16.44%), HBV in 35 (11.53%), HCV in 16 (5.26%), Cryptogenic cirrhosis [CC] in 16 (5.26%), Autoimmune liver disease in 7 (2.30%) [including autoimmune hepatitis [AIH] in 5 (1.64%), AIH + PSC overlap in 1 (0.32%), autoimmune cholangitis in 1 (0.32%)], Metabolic causes in 6 (2.0%) [Including Wilson's disease [WD] in 4 (1.31%), Galactosemia in 1 (0.32%), Tyrosinemia in 1 (0.32%)], and Budd-chiari syndrome in 3 (0.98%). This is tabulated in table 1.

Table 1: Etiology of cirrhosis (n=304)

Etiology	No. (%)
Alcohol	105 (34.53)
NAFLD	66 (21.71)
Cryptogenic (Probable NAFLD)	50 (16.44)
HBV	35 (11.53)
Cryptogenic cirrhosis	16 (5.26)
HCV	16 (5.26)
Autoimmune Hepatitis	5 (1.64)
Wilson's Disease	4 (1.31)
Budd-Chiari syndrome	3 (0.98)
AIH+ PSC overlap	1 (0.32)
Galactosemia	1 (0.32)
Tyrosinemia	1 (0.32)
Autoimmune Cholangitis	1 (0.32)

Relation of gender and etiology: Gender had significant relation with etiologies of cirrhosis: Alcohol [105 (34.53%) vs. 0] was significantly common in males, whereas Cryptogenic [39 (17.97%) vs. 27 (31.03%)], AIH [3 (60%) vs. 2 (40%)], HBV [21 (9.67%) vs. 14 (16.09%)] and HCV [7 (3.22%) vs. 9 (10.34%)] were common in females. This is tabulated in table 2.

Table 2: Relation of gender with etiology of cirrhosis among non alcoholic patient:

Etiology	Total (%)	Male (%)	Female	p-value
Cryptogenic	16 (5.26)	6 (2.76)	10 (11.49)	0.11
Cryptogenic (Probable NAFLD)	50 (16.44)	33 (15.2)	17 (19.54)	0.10
HBV	35 (11.47)	21 (9.67)	14 (16.09)	0.62
HCV	16 (5.24)	7 (3.22)	9 (10.34)	0.29
AIH	5 (1.96)	2 (0.92)	3 (3.4)	0.45
WD	4 (1.63)	3 (1.38)	1 (1.14)	0.44
BCS	3 (1.31)	1 (0.4)	2 (2.29)	0.41
AIH+PSC	1 (0.32)	1 (0.4)	0	-
Galactosemia	1 (0.32)	0	1 (1.14)	-
Tyrosinemia	1 (0.32)	0	1 (1.14)	-
Autoimmune cholangitis	1 (0.32)	0	1 (1.14)	-
Total	**304 (100)**	**112 (51.61)**	**87 (28.6)**	**-**

Table 3: Age wise distribution of etiological spectrum of cirrhosis:

Age [year]	<20 (%)	20-30 (%)	30-40 (%)	40-50 (%)	50-60 (%)	>60 (%)
Alcohol	0	6 (31.5)	29 (67.4)	40 (50.3)	24 (31.6)	6 (8.4)
NAFLD	0	1 (5.2)	0	5 (11.3)	28 (35.4)	32 (45.1)
Cryptogenic (Probable NAFLD)	0	0	0	19 (24.1)	11 (13.9)	20 (28.1)
Cryptogenic	4 (30.7)	4 (21)	7 (16.2)	1 (1.2)	0	0
HBV	0	5 (26.3)	4/43(9.3)	10 (12.6)	6 (7.5)	10 (14.1)
HCV	0	0	0	3 (7.5)	8 (10.1)	5 (7.1)
AIH	0	0	2 (4.6)	1 (1.2)	2 (2.5)	0
WD	2 (15.3)	2 (10.5)	0	0	0	0
BCS	2 (15.3)	0	1 (2.3)	0	0	0
AIH+ PSC	1 (7.6)	0	0	0	0	0
Galactosemia	1 (7.6)	0	0	0	0	0
Tyrosinemia	1 (7.6)	0	0	0	0	0
Autoimmune Cholangitis	0	1 (5.2)	0	0	0	0

Relation of age and etiology: Age has significant relation with following etiologies: alcohol, HBV, HCV, cryptogenic (probable NAFLD), CC, Wilson's disease, AIH, Budd-Chiari syndrome: WD was common before 30; Alcohol and HBV after 30; HCV after 50 and NAFLD after 60 years of age. Alcohol: < 30 years: 6/105, > 30 years 99/ 105 patients; HBV: < 30 years: 5/35, > 30 years: 30/ 35 patients; HCV: < 50 years: 3/16, > 50 years: 13/ 16 patients; NAFLD: < 60 years: 32/66, > 60 years: 34/ 66 patients; WD: < 30 years: 4/4, > 30 years: 0/ 4 patients; Autoimmune liver disease: <20 years: 2/7, >20 years: 5/7; Cryptogenic (probable NAFLD): < 50 years: 19/50, > 50 years: 31/ 50 patients. HBV, HCV and NAFLD were not responsible for cirrhosis below the age of 20 yrs. This is tabulated in table 3.

Table 4: Significant cut off age for various etiologies of cirrhosis

Etiology	Cut off age (In years)
Alcohol	30
Cryptogenic (Probable NAFLD)	50
HBV	30
HCV	50
NAFLD	60

Significant cut off age for various etiologies of cirrhosis: We suggested the cut off age for various etiologies of cirrhosis on the basis of maximum number of patients found in that particular age group. Alcohol and HBV was commoner after age of 30 years, AIH in age range of 20-40 years; HCV and CC-NAFLD after age of 50 years and NAFLD after age of 60 years. This is shown in table 4.

DISCUSSION

Various etiologies contribute to development of cirrhosis and later HCC, viral hepatitis and alcohol being commonest. Epidemiology of liver cirrhosis is different in parts of the world; with marked differences between age, gender, ethnicity and geographical areas. Prevalence, nature and time of acquisition of the major risk factors for cirrhosis like HBV, HCV and alcohol may partially explain this.[11] There are regional differences in relative contributions of these individual etiologies in development of cirrhosis.[12-17] An understanding of these variations is very important in developing public health and preventive strategies. Efforts at all levels of health care i.e. government, health care agencies, health care professionals and pharmaceutical agencies will be needed to curtail increasing burden of chronic liver disease and related mortality throughout the world.[1,18]

Contrary to global perception, alcohol is a predominant etiology of cirrhosis in Western India. Alcohol

contributed to 34% of cirrhotics in our study, the figure was even higher for males (48%). According to previous study in 2000, alcohol was considered to be responsible for 32% of all cirrhosis worldwide.[19] Recent increase in cirrhosis mortality in UK is thought to be due to increased alcohol consumption in last few decades, which might be reflection of easy availability of alcohol in market, relaxation in alcohol policies and heavy effect of advertisements.[1,20] In our study, alcohol is the most common etiology of cirrhosis even in the state where it is prohibited by law.

Globally, HBV contributed to 30% and HCV to 27% of cirrhosis, as per recent estimate in 2006.[18] Previous estimates have suggested 51% for HBV and 17% for HCV.[18,21] Previous small-scale estimates from North India for relative contribution of viral etiology to cirrhosis suggested that HBV was responsible for 25-31%, HCV for 14-28% and combined HBV-HCV 2-9% of cirrhosis.[22,23] In a small study from western India, HBV contributed to cirrhosis in 16%, HCV in 11% and combined HBV- HCV in 2% patients.[24] Our study suggested around 11% for HBV and around 5% for HCV which was lower than previous figures.

NAFLD is the most common etiology for cirrhosis, surpassing both HBV and HCV. Rising prevalence of obesity and diabetes, adoption of western life styles, high calorie diet and sedentary habits are responsible for upcoming epidemic of NAFLD in our country.[25] Prevalence of NAFLD in India is estimated around 5-28% of general population and 6-30% of all chronic liver disease in various series.[26] In Accordance to previous series, most cases of CC were due to burnt-out NAFLD. Metabolic, autoimmune and vascular etiologies were seen in few patients.

Preventable etiologies like alcohol, HBV and HCV were present in around 50%. Vaccination for HBV, safe blood, safe sex and safe injection practice, early treatment for these viral infections, awareness among general population as well as medical-paramedical staff and widespread screening programmes can prevent further spread of viral etiology of cirrhosis.[18] Awareness and education of life style, food, exercise and activity might help in curtailing burden of alcoholic as well as NAFLD as cause of cirrhosis.

Cirrhosis can occur at any age and often causes prolonged morbidity. It is generally believed that cirrhosis occur much less frequently in young adults than in older patients. In our findings, the duration of alcohol consumption was found to be significantly higher in adult of age group of 30 years. Among older patients, cryptogenic causes of cirrhosis were greater as compared to younger patients. Genetic factors may likely to play a role in making patients more susceptible to NAFLD, and consequently cryptogenic/NAFLD/NASH cirrhosis.[27] Cirrhosis caused by HCV was also presented at an older age (50 years). It is possible that environmental factors may explain this finding, such as differential age at exposure to HCV, but epidemiologic data supporting this possibility are lacking.

In conclusion, NASH (proven & unproven) was the most frequent etiologic factor for the development of cirrhosis. This mostly develops in diabetes and obese people. NASH can be prevented only with the control of CHO and Lipid content in their diet. Even though, regular exercise may also help to workout in those patients who have their sedentary life. The second most common etiological factor in the development of liver cirrhosis was Alcohol intake. Alcohol intake was seen mostly in men as compared to female. Patient may develop Hepatocellular Carcinoma in later stages. Therefore, awareness must be created to avoid alcohol intake. It would be helpful in prevention of any type of liver disease including cirrhosis and HCC. Alcohol intake problem should be handled by the local health advisors and religious leaders. Other minor etiological factor includes HBV and HCV followed by Metabolic, autoimmune and vascular etiologies in few patients. Most etiologies have peculiar age distribution. The early diagnosis of above mentioned disease conditions may prevent the progression of disease severity and may also prevents the cirrhosis.

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