ANALYSIS OF LIVER CIRRHOSIS IN A PATHOLOGY LABORATORY; AETIOLOGY, RISK FACTORS AND HISTOPATHOLOGICAL PATTERNS

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Abstract

Background: Cirrhosis of the liver is a major risk factor for the development of hepatocellular cancer. Its prevalence is significantly modified and determined by aetiological factors prevalent in a particular locality. This study seeks to analyze the aetiology and risk factors associated with liver cirrhosis in a pathology laboratory in Northern Nigeria.

Methods: This is a ten year analysis of liver cirrhosis in the department of Pathology Ahmadu Bello University Teaching Hospital, Zaria, Nigeria. Biopsies were fixed in formalin, embedded in paraffin. Histology slides stained with H&E, PAS and mucicarmine were studied.

Results: Sixty – five cases of liver cirrhosis were analysed. The peak age was in the 5th decade with a male to female ratio of 1.7:1. Macro-nodular histologic variant accounted for 89.2% while 29.2% cases were associated with hepatocellular carcinoma. Common implicated aetiological factors were HBV infection in 26 (40.0%) cases, HCV in 6 (9.2%) cases and HBV/HCV co-infection in 8 (12.3%) cases. Biliary atresia accounted for 3(4.6%) cases in children aged 3 to 7 months with a female preponderance.

Conclusion: It was confirmed that viral infection is the predominant aetiological agent of liver cirrhosis in our setting. Key words: Liver cirrhosis, macronodular, hepatitis B viral hepatitis

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INTRODUCTION

Liver cirrhosis has long been regarded as the final common pathway of various chronic liver diseases. It is the twelfth most common cause of death and accounts for a significant proportion of liver-related deaths. World Health Organization (WHO) reports that liver cirrhosis accounted for 1.8% of all deaths in Europe.¹ Cirrhosis of the liver is a major risk factor for the development of hepatocellular carcinoma (HCC) and constitutes a major burden of liver morbidity. In Bangladesh, Gani *et al*² reported 77% of their patients with hepatocellular carcinoma suffered from cirrhosis while Hyasinta J *et al*³ from Tanzania reported the presence of cirrhosis coexisting with HCC in 66.2% of their cases. There is a great variability in the prevalence of cirrhosis in Nigeria as in other parts of sub Saharan Africa. This variability is significantly determined by the aetiological or predisposing factors leading to chronic liver disease in particular locality.

The common aetiological factors implicated in cirrhosis from the vast majority of patients with liver disease worldwide are chronic viral hepatitis or steato-hepatitis associated with either alcohol or obesity. Other aetiologies include parasitic infestation such as schistosomiasis, autoimmune attack on hepatocytes or biliary epithelium, neonatal liver disease, metabolic disorders including Wilson's disease, hemochromatosis and a variety of storage disorders.⁴ In developed nations like Europe and United states of America (USA), non- alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) were the most common implicated risk factors, while in sub-Saharan Africa and Asia infectious aetiology predominated.^{4,5}

There is a significant change in the natural history of cirrhosis in recent years owing to marked advancement in the clinical monitoring and advances in the treatment modalities of chronic liver diseases in relation to aetiological factors. Identification of inciting agent can be made possible from clinical history, presence of serological markers of the agent and morphologic evaluation of the tissue histo-pathologically for on-going activity and disease progression. The level of necro-inflammation in

histological sections is an accurate marker of on-going activity while the presence of fibrosis assesses the disease progression.⁷ This study seeks to analyze the risk and aetiological factors associated with liver cirrhosis in a pathology laboratory in Northern Nigeria.

MATERIALS AND METHODS

This is a 10 - year analysis of liver cirrhosis in the department of Pathology Ahmadu Bello University Teaching Hospital, Zaria. The liver biopsies were fixed in formalin, embedded in paraffin and stained with haematoxylin and eosin (H&E), Masson's trichrome, Reticulin, Periodic acid-Schiff (PAS) with and without Diastase digestion, Pearls and Shikata orcein. Demographic data on age and sex were extracted from the accompanied case card. Clinical history of alcohol ingestion, serological markers of infection and viral activity were also retrieved from case files. In addition to the viral markers and clinical history, aetiological factors leading to cirrhosis were considered histologically as post HBV hepatitis cirrhosis with presence of ground glass hepatocytes with or without activity and presence of viral inclusion identified with orcein stain or HCV with presence of lymphoid aggregates with steatosis. Autoimmune hepatitis cases were identified by marked plasma cells infiltrates while alcoholic cirrhosis showed steato-hepatitis and Mallory bodies.

RESULTS

Three hundred and one liver biopsies were analysed and of these 65 were liver cirrhosis cases. They formed 21.6% of all the chronic liver diseases diagnosed during the study period. There were 41 males and 24 females with a male to female ratio of 1.7:1 and peak age was in the fifth decade of life (Fig.1). Histologically, macronodular cirrhosis accounted for 89.2% (58 cases) while micronodular and mixed pattern constituted 10.8% and 29.2% cases respectively. Hepatotrophic viruses accounted for the bulk of aetiological factors (Table 1) with hepatitis B viral (HBV) infection seen in 26 (40.0%) of the cases, HCV in six (9.2%) and HBV/HCV co-infection in eight (12.3%) cases. Biliary type cirrhosis secondary to biliary atresia accounted for three (4.6%) of cases and this was seen in children aged

three to seven months with a female preponderance. Three cases were associated with significant alcohol consumption and two of them showed micronodular pattern of cirrhosis while one showed mixed macro and micronodular pattern of cirrhosis. There were 19 (29.2%) cryptogenic cases because there was absence of identifiable risk factor.

DISCUSSION

Liver cirrhosis is an important liver disease which accounted for 21.6% of chronic liver diseases seen during the study period. The predominant morphologic pattern was that of macronodular due to the nature of inciting agents causing the liver fibrosis with subsequent progression to cirrhosis. This explains the marked variability in the prevalence of cirrhosis globally and in Nigeria. Lawan and Ogunbiyi⁸ in Ibadan and Nwokediuko *et al*⁹ in Enugu reported rates of 23.4% and 20.4% respectively similar to our findings. These rates are slightly higher than earlier report of 18.8% from Ibadan¹⁰ and 17.7% reported by Abdulkareem *et al*¹¹ in Lagos. Higher rates of 30.8% and 41.4% were reported from Jos and Ife respectively.^{12,13} The higher rate in Jos was attributed to high rate of consumption of locally brewed alcohol from grains with high aflatoxin content. The lowest rates of 6.3%, 13.6% and 13.9% were reported in Benin, Kano and Ilorin respectively.¹⁴⁻¹⁶

Hepatotropic viruses accounted for a significant 61.5% of aetiological in this study with post HBV hepatitis constituting 40.0%, HCV hepatitis 9.2% and HBV and HCV co-infection 12.3%. The HBV hepatitis is highly endemic in Africa with prevalence of 8%¹⁷ and sero-prevalence of HBsAg in Nigeria ranges from 10% to 40%.¹⁸ In 2014, Mbaawuaga *et al*¹⁹ reported a 12.0% seroprevalence of HBsAg in 1535 randomly collected blood specimens from different groups of subjects in Benue State located in North central Nigeria. Musa *et al*²⁰ also studied 46 published articles in a 13years systematic review and meta- analysis of the prevalence of HBV infection in Nigeria and reported a range of 0.5% to 46.8% and a pooled prevalence of 13.6% among Nigerians.

Chronic HBV hepatitis is associated with marked necro-inflammatory activity and progressive fibrosis during active viral replication. Similar to findings in this study, HBV hepatitis was the predominant cause of cirrhosis in Ibadan, Enugu, Jos, Kano and Ilorin. In fact, Samaila *et al* in Kano reported a 100% prevalence of HBV in liver cirrhosis cases.^{8,9,13-15}

HCV is relatively uncommon in our environment, but increasing prevalence associated with liver cirrhosis has been reported. Laraba *et al*²¹ in Maiduguri reported prevalence rate of 12.1%, while In Ibadan Ola *et al*²² reported higher rate of 20% among patients with liver cirrhosis. However, a lower HCV prevalence rate of 4.3% among patient with liver cirrhosis was reported by Lawan *et al*⁸ in Ibadan. Elfaki *et al*²³ in their study of patients with liver cirrhosis in Western Sudan documented a prevalence rate of 1.5%. In a ten year study of 22,450 Egyptian patients with chronic liver diseases, 5.9% had hepatocellular carcinoma (HCC) and unlike in other African countries, 72.3% of these were HCV post-cirrhotic and only 20.4% were HBV infection sero-positive. This finding is not surprising because Egypt has the highest HCV prevalence in the world.^{24, 25} In the general United States of America population, it has been estimated that 1.3% were chronically infected with HCV of which 10%-20% will

develop liver cirrhosis with 1-5% progressing to hepatocellular carcinoma within 20-30 years of infection.²⁶

HBV and HCV co-infection were recorded in 12.3% of our study. Patients with more than two predisposing factors exhibit rapid progression of the disease process with eventual progression to cirrhosis. The common aetiological factors in US and Europe were NAFLD, ALD and HCV infections.⁵ Chronic infection with HCV is an important co-morbidity in the progression of alcoholic liver disease to cirrhosis in chronic and excessive drinkers. Even moderate alcohol intake of 20-50 g/d increases the risk of cirrhosis and hepatocellular cancer in HCV-infected individuals.⁴ Patients with both alcoholic liver injury and HCV infection develop decompensated liver disease at a younger age and have poorer overall survival. Increased liver iron stores and rarely, porphyria cutanea tarda can occur as a consequence of the overlapping injurious processes secondary to alcohol abuse and HCV infection. In addition, alcohol intake of more than 50 gm/d by HCV-infected patients decreases the efficacy of interferon-based antiviral therapy.^{4,5}

The macronodular morphologic pattern of cirrhosis seen in this study is secondary to chronic viral hepatitis and 89.2% had macronodular form of cirrhosis. This confirms that viral infection is the predominant aetiological agent in our setting. Micronodular cirrhosis usually caused by alcohol, hemochromatosis, cholestatic cirrhosis and hepatic venous outflow obstruction is not common in our setting as seen in this study with only 4.6% of our cases related to excessive alcohol consumption. This finding is comparable to the report of 5.7% by Adeniji *et al*¹⁵ in Ilorin.

Increasing number of patients with liver cirrhosis may progress to development of hepatocellular carcinoma. In this study 29.2% had associated hepatocellular carcinoma. This is similar to the reports of 28.2% in Jos and 27.7% in Ibadan though lowers than the 43% reported by Adbulkareem *et al* in Lagos.^{8,11,13} Liver cirrhosis is an established premalignant condition for the development of hepatocellular carcinoma. The mechanism for this progression to cancer is due to continuous inflammation and hepatocyte regeneration in the setting of chronic hepatitis and chromosomal damage which initiates hepatic carcinogenesis.²⁴

Overall, 57% of all cirrhosis were attributable to either HBV (30%) or HCV (27%) infection with resultant mortality of 446,000.²⁷

Cirrhosis involves scarring and regenerations, and different aetiologies cause different patterns of these processes at different rates of progression. Also, within each disease entity, the level of architectural distortions and the resultant clinical implications vary in severity among patient over time. There is indeed a wide range of clinical spectrum of cirrhosis ranging from absence of disease burden regular daily activities typical of cirrhosis due to non-alcoholic steatohepatitis (NASH) to severe illness seen in cirrhosis from chronic HCV hepatitis with complications ranging from portal hypertension, hepatic encephalopathy to the development of hepatocellular carcinoma. Finally there are similarities among cirrhotic livers of different aetiologies at the cellular level.⁶

In conclusion therefore, it was confirmed that viral infection is the predominant aetiological agent of liver cirrhosis in our

setting. It is strongly recommended that efforts be put in place for the prevention of viral hepatitis infections in all communities in Nigeria through free and regular childhood immunization.

Fig. 1: Line graph showing age distribution of liver cirrhosis cases

Table 1: Aetiological Factors associated with Cirrhosis from Clinical History, Serological Tests and Morphologic Features

Aetiologic Factor	Male	Female	Total (%)
Biliary atresia	1	2	3 (4.6)
HBV Infection	18	8	26 (40.0)
HCV Infection	4	2	6 (9.2)
HBV/HCV Co.infection	6	2	8 (12.3)
Alcohol	3	0	3 (4.6)
Cryptogenic	9	10	19 (32.6)
Total	41	24	65 (100)

Figure 3: secondary biliary cirrhosis showing proliferating bile ductules with cholestasis

Figure 2: low power view of liver cirrhosis showing irregular

nodules formed by thick band of fibrous tissues. MT x 100 magnification

Figure 2b: high power view of liver cirrhosis showing irregular nodules formed by thick band of fibrous tissues. MT x 400 magnification

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