EASTERN VIEW OF HEPATIC CIRRHOSIS AND ITS ETIOLOGY

Sarwar J. Zuberi, Tariq Z. Lodi, Rashida Maqsood, Khushnaseeb Ibrahim, Saad M. Khan

Abstract

One hundred and ten patients with cirrhosis of the liver were studied. There were 70 males and 40 females. Their mean age was 43.9 years. They were more than a decade younger than the patients in the West. The main clinical signs were hepatosplenomegaly, ascites and jaundice. The stigmata of cirrhosis i.e., Palmar erythema, Spider angioma, Teticular atrophy and gynaecomastia were less frequent.

Histologically 89% had post-necrotic (macronodular) 7.3% nutritional (micronodular) and 3.6% post hepatitic cirrhosis.

Morphological pattern and frequency of hepatitis B antigen in general population and in patients with cirrhosis, points towards the hepatitis virus as the most likely etiological factor.

PMRC Research Centre, Jinnah Postgraduate Medical Centre, Karachi-35.

Introduction

Cirrhosis of the liver is a common clinical entity. Its morphological characteristics and etiology varies in different geographical areas. Karachi being a metropolitan city is inhabited by various ethnic groups and a fair number of individuals come to the city from rural areas for medical treatment. Most people coming to public hospitals belong to the lower socio-economic group. They live in thickly populated areas with unhygienic surroundings. Intake of alcohol in our patient population is not as common as in the West and cases of viral hepatitis are seen all the year round. There is also some evidence of contamination of food with fungal toxins. This study was conducted to determine the clinical, biochemical and morphological pattern of cirrhosis and the most probable etiology of the disease.

Material and Methods

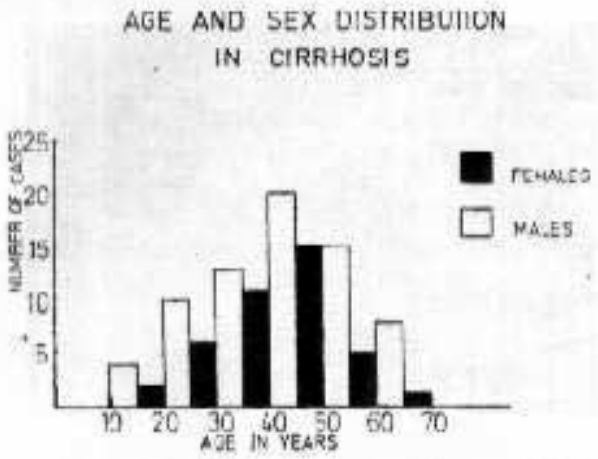
One hundred and ten cases of clinically diagnosed patients with cirrhosis of the liver admitted to the medical wards of Jinnah Postgraduate Medical Centre between March 1973-June 1977 were studied. Each patient was evaluated according to a protocol and a liver biopsy was performed.

Investigations included haemoglobin, total and differential leucocyte count, platelets count, Prothrombin time, liver function tests, serum protein electrophoresis and BSP infusion studies. Sera were also tested for hepatitis Bs antigen using CIEP.

Results

Age and Sex:

There were 70 males and 40 females. Their ages ranged from 17 to 71 years (Mean ± S.E. 43.9 ± 1.2). The age distribution is shown in Fig. 1.



Clinical features:

The presenting symptoms are shown in Table I. The main presenting symptoms were ascites, abdominal pain and jaundice. Sixteen (40%) of 40 females below the age of 40 years had amenorrhoea.

Table I: Symptoms.

Symptoms	*No. of patients*	*Percent*
Abdominal swelling (Ascites)	65	59.09
Abdominal pain	61	55.45
Jaundice	54	49.04
Anorexia	48	43.64
Oedema	44	40.00
Fever	39	35.45
Loss of weight	35	31.82
Fatigue	32	29.09
Bowel disturbances	25	22.73
Nausea and vomiting	24	21.82
Others	24	21.82
Gastrointestinal bleeding	20	18.18
General Malaise	16	14.55
Arthralgia	9	8.18
Coma	2	1.82

There was a past history of jaundice in 56 (59.9%), a history of jaundice in closer relatives in 8(7.2%) and alcohol intake in 8(7.2%) cases. Twelve (10.9%) had blood transfusions in the past and 6(5.5%) had diabetes.

Table II: Physical Findings.

Physical findings	*No. of patients*	*Percent*
Hepatomegaly	72	65.4
Ascites	71	64.5
Splenomegaly	62	56.4
Jaundice	58	52.7
Oedema	33	30.0
Abdominal wall veins	25	22.7
Palmar Erythema	18	16.3
Spidernaevi	16	14.5
Sparse body hair	11	10.0
Clubbing	10	9.0
Gynecomastia	5	4.8
Testicular atrophy	2	1.8

The physical signs are shown in Table II. The most prominent signs were hepatosplenomegaly, ascites and jaundice. The usual stigmata (spider naevi sparse body hair, testicular atrophy and gynecomastia) of cirrhosis were infrequently seen in this study.

Hypertension which is known to be rare in cirrhosis (Spatt and Rosenblatt, 1949; Loyke, 1955) was observed only in 5(4.5%) of cases, while its frequency in general population is 10-15% (Hashmi).

Investigations:

Table III shows the haematological findings. The haemoglobin ranged between 3.8 to 18.5G%. Fifty-nine patients had anaemia (Hb < 11G%) and the haemoglobin was normal in the remaining 49 patients. Anaemia in all the cases was of hypochromic type. Nineteen cases had leucopenia (WBC less than 5000/cmm), 3 Leucocytosis and the remaining 85 had a normal leucocyte count. The platelet count varied from 11,000 to 463,000/cmm (Mean 123,500/cmm). Prothrombin time was increased in 27 cases.

Table III: Haematological Investigations.

Investigations	*No. tested*	*Mean ± S.E.*
Haemoglobin	108	11.3 ± 0.27
Leucocyte Count	107	6107 ± 277.95
Platelet Count	110	123500.0 ± 6100.0
Prothrombin time	110	21.26 ± 0.9

The results of biochemical investigations are shown in Table IV. The bilirubin was normal in 37, alkaline phosphatase in 15, SGOT in 8 and SGPT in 45 cases. Albumin levels below 3.5G% were found in 45 and globulin levels above 3.2G% in 47 cases.

Serum protein electrophoresis was done in 50 patients. The results are shown in Table V. Two patients were found to have alpha$_1$ globulin deficiency and the mean gammaglobulin level was 2.45G%.

Thymol turbidity ranged from 4 to 20 Maclagen units.

BSP infusion studies (Wheeler et al., 1960) were done in 9 healthy subjects and 8 patients with cirrhosis of the liver. The Mean ± SD of Tm (Transport Maximum)in control subjects was 8.4 ± 3.08 and S(storage) 44.4 ± 30.88. In the patients TM was 2.38 ± 1.10 and S, 39.73 ± 9.77.

Sera of 22 of 83 patients (26.5%) were positive for hepatitis Bs antigen.

Table IV: Biochemical Investigations.

Investigations (Normal Range)	*No. tested*	*Mean ± S.E. (Range)*
Total bilirubin (mg%) (0.2—1)	106	3.3 ± 0.46 (0.2—17)
Conjugated Bilirubin (mg%) (0—0.3)	105	2.1 ± 0.29 (0.1—13)
Unconjugated Bilirubin (mg%)	105	1.3 ± 0.29 (0.0—7.6)
SGOT (mu/ml) (0—12)	107	33.53 ± 2.41 (8—140)
SGPT (mu/ml) (0—12)	108	15.11 ± 2.05 (2—75)
Alk. Phosphatase (Sigma units) (0.8—3.1)	109	6.19 ± 0.45 (0.84—21.9)
Thymol turbidity (Maclagenunto) (0—4)	56	7.58 ± 0.59 (4—20)
Total protein (G%) (6—8)	101	7.0 ± 0.08 (5.2—8.7)
Albumin (G%) (3.5—6)	101	3.27 ± 0.08 (1.8—5.4)
Globulin (G%) (1.5—3.2)	101	3.77 ± 0.09 (1.6—5.4)

Table V: Electrophoretic Pattern in Cirrhosis.

Investigations	*Mean ± S.E. (Range)*
Total protein (G%)	7.15 ± 0.10 (6.0—8.6)
Albumin (G%)	3.10 ± 0.10 (1.9—4.6)
$Alpha_1$ Globulin (G%)	0.26 ± 0.02 (0—0.55)
$Alpha_2$ Globulin (G%)	0.55 ± 0.04 (0.15—1.26)
Beta Globulin (G%)	0.78 ± 0.04 (0.15—1.63)
Gamma Globulin (G%)	2.45 ± 0.13 (1.0—4.27)

Histological Types:

The cases were classified according to the criteria of Anthony et al. (1977). Eighty nine (89%) had postnecrotic (macronodular, Type A) cirrhosis (Fig. 2), 8(7.3%) had nutritional (micronodular Type C) cirrhosis (Fig. 3) and the remaining 4(3.6%) had post hepatitic (incomplete Septal, Type B) cirrhosis.

Follow-up:

Seventy-one patients were followed up from 2 weeks to 177 weeks (average 89.5 weeks).

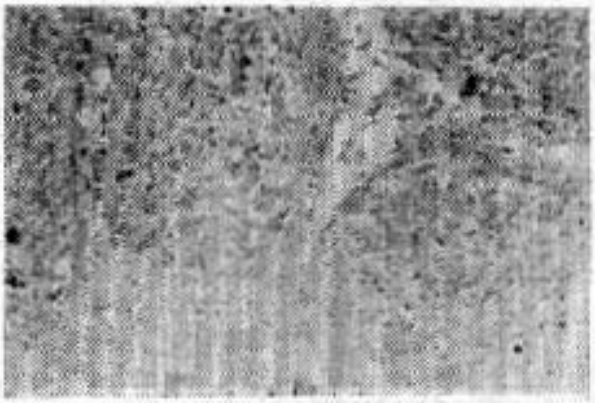


Fig. 2:-Macronodular cirrhosis showing macronodules and thick septa (H & EX 78).

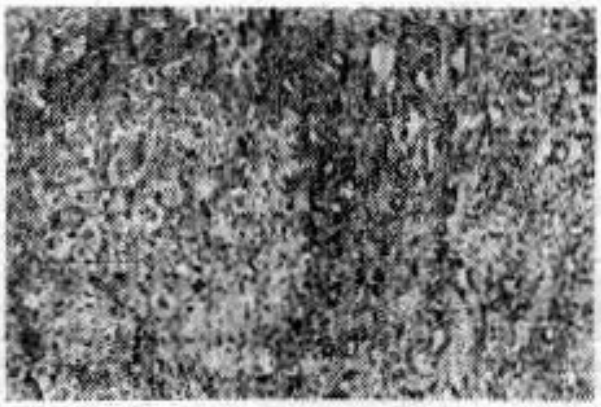


Fig. 3:-Micronodular cirrhosis showing micronodules, proliferation of bile duct and mild piecemeal necrosis (H & EX 78).

Of 69 patients with enlarged liver, 4 had some regression in hepatic size. Reduction in the size of spleen was observed only in 2 out of 62 cases. The time taken for various biochemical parameters to return to normal is shown in Table VI.

Table VI: Follow up

Biochemical features	*Number of cases*	*Time taken to return to normal (Weeks) Mean ± S.E.*
Bilirubin to return to normal	16	4.69 ± 1.24
SGOT to return to normal	11	5.82 ± 1.76
SGPT to return to normal	15	11 ± 5.82
Globulin to return to normal	14	11.36 ± 4.34

Three patients had splenectomies for hypersplenism.

Of the entire group, 5 patients are known to have died. Three of the five had hepatic encephalopathy and 2 massive gastrointestinal bleeding.

Discussion

Compared with the West cirrhosis in the East appears to be an etiologically and clinically a different disease.

Although the male predominance is universal, the patients in the eastern series (Borhanmanesh et al., 1971; Radha Krishna Rao, 1933; Fernando et al., 1948) are a decade or two younger than those in western countries (Stone et al., 1968; Fagin and Thomspon, 1944; Ratnoff and Patek, 1942).

Splenomegaly is more frequent in eastern series. Eightysix per cent of the cases reported from Iran (Borhanmanesh et al., 1971), 67% from Iraq (Paton and Rassam, 1975) and 56.3% in this series had an enlarged spleen. The size of the spleen varied from 3 to 16.5 cms.

Hepatomegaly was more frequent in this series than those reported by Borhanmanesh et al. (1971) from Iran, Stacey (1944) from Iraq and Fernando et al. (1948) from Ceylon.

The stigmata of cirrhosis like spider angioma, Palmar erythema, gynaecomastia, sparse body hair, testicular atrophy and Dupuytren's contracture were not as frequent as in the series reported from the West (Summerskill et al., 1960; Garceau et al., 1963).

Clubbing of fingers was observed in 9% in this series as has previously been reported by Borhanmanesh et al. (1971) and Ratnoff and Patek (1942).

Morphologically, cirrhosis in Pakistan is mostly of Macronodular type while a few cases of nutritional (micronodular) and post hepatitic type are also seen. The findings are in contrast to those reported by Gall (1960) and Stone et al. (1968).

The morphological pattern and local habits make alcohol as an unlikely cause of cirrhosis in this country.

Aflatoxin has been related to cirrhosis (Rees 1966; Amla 1970). Contamination of food with Aflatoxin has been reported in this country (Nizami and Zuberi, 1977) but the characteristic features of cirrhosis due to mycotoxins with reverse lobulation (Tandon et al., 1977) have not been observed in this series.

The frequency of hepatitis B antigen in a population determines the prevalance of hepatitis and chronic liver diseases. Hepatitis B antigenaemia was found in 3.6% of apparently healthy adults (Quraishi et al., 1978) and 22% of these showed evidence of hepatitis in liver biopsies (Ahmad et al., 1978). These findings suggest a significant quantum of asymptomatic liver disease in our population.

Hepatitis Bs antigen has been more frequently found in cirrhosis in eastern countries. Boxall et al. (1976) detected HBsAg in 3% cases of cirrhosis in Birmingham and 26.5% in Iraq. In this series 26.5% cases of cirrhosis had HBs antigenaemia. As in Iraq (Paton and Rassam, 1975), this study also shows a striking hypergammaglobulinaemia, in the absence of recognised immunological liver disease.

In the absence of alcohol and other possible causes of cirrhosis, a relatively high frequency of HBs antigenaemia in healthy population and patients with liver disease and a fair amount of asymptomatic liver disease, it is postulated that hepatitis virus may be playing some etiological role in the chronic liver disease in Pakistan.

Acknowledgements

Referral of cases by the Professorial and resident staff of the department of Medicine, review of slides by Prof. N.A. Jafarey, help in clinical evaluation by Drs. T.J. Hassan and F. Samad and the secretarial assistance of Mr. Laeeq Ahmad is gratefully acknowledged.

References

Ahmad, M., Quraishi, M.S., Zuberi, S.J. (1978) Liver disease in asymptomatic antigen negative individuals. JPMA., 28:57.

Amla, I., Kamala, C.S., Gopalakrishna, G.S., Jayraj et al. (1970) Cirrhosis in children from peanut meal contaminated by aflatoxin. Am. J. Clin. Nut., 24:609.

Anthony, P.P., Ishak, K.G., Nayak, N.C., Poulsen, H.E. and Scheuer, P.J. (1977) The morphology of cirrhosis: definition, nomenclature, and classification. Bull. World Health Org., 55:521.

Borhanmanesh, F., Ghavami, A., Dutz, W. and Bagheri, S. (1971) Cirrhosis of the liver in Iran. A prospective study on 66 cases. J. Chronic Dis., 23:891.

Boxall, E.H., Flewett, T.H., Paton, A. and Rassam, S.W. (1976) Hepatitis-B surface antigen and cirrhosis in Iraq. Gut, 17:119.

Fagin, I.D. and Thompson, F.M. (1944) Cirrhosis of liver. An analysis of 71 Cases. Ann. Intern. Med., 21:285.

Fernando, P.B., Medonza, O.R. and Rajasuriya, P.K. (1948) Cirrhosis of liver in Ceylon and its relation to diet; review of 102 cases. Lancet, 2:205.

Gall, E.A. (1960) Posthepatitic, postnecrotic, and nutritional cirrhosis. A Pathological analysis. Am. J. Path., 36:241.

Garceau, A.J., Chalmers, T.C. and Boston Inter-Hospital Liver Group (1963) The natural history of cirrhosis I. Survival with oesophageal varices. N. Engl. J. Med., 268:469.

Hashmi, J.A.—Personal Communication.

Loyke, H.F. (1955) The relationship of cirrhosis of the liver to hypertension—A clinical and experimental review. Amer. J. Gastroent., 38:56.

Nizami, H.M., Zuberi, S.J. (1977) Aflatoxin and liver cancer in Karachi. JPMA., 27:351.

Paton, A. and Rassam, S.W. (1975) A Geographical view of cirrhosis. JPMA., 25:3.

Qurashi, M.S., Zuberi, S.J. and Ahmed, M. (1978) Hepatitis Bs antigenaemia. Incidence in apparently healthy adult males. JPMA. 28:56.

Radhakrishna Rao, M.V. (1933) An Investigation into decompensated portal cirrhosis. Indian J. Med. Res., 21:389.

Ratnoff, O.D. and Patek, A.J. Jr. (1942) The natural history of baennec's cirrhosis of liver. An analysis of 386 cases. Medicine, 21:207.

Rees, K.R. (1966) Plant toxins and human disease. The mechanism of action of aflatoxin in producing acute liver necrosis. Proc. Roy. Soc. Med., 59:755.

Spatt, S.D. and Rosenblatt, P. (1949) The incidence of hypertension in portal cirrhosis. A study of eighty necropsied cases of portal cirrhosis. Ann. Intern Med., 31:479.

Stacey, R.S. (1944) Portal cirrhosis in Iraq. Trans. Roy. Soc. Trop. Med. Hyg., 37:387.

Stone, W.D., Islam, N.R.K. and Paton, A. (1968) The natural history of cirrhosis; experience with an unselected group of patients. Quart. J. Med., 37.119.

Summerskill, W.H.J., Davidson, C.S., Dible, J.H., Mallory, K., Sherlock, S., Turner, M.D. and Wolfe, J. (1960) Cirrhosis of liver. A study of alcoholic and nonalcoholic patients in Boston and London. N. Engl. J. Med., 262:1.

Tandon, B.N., Krishna-Murthy, I., Koshy, A. et al. (1977) Study of an epidemic of Jaundice, presumably due to Toxic hepatitis in North West India. Gastroenterology, 72:488.

Wheeler, H.O., Meltzer, J.I. and Bradley, S.E. (1960) Biliary transport and hepatic storage of sulfobromophthalein sodium in the unanaesthetized dog, in normal man, and patients with hepatic disease. J. Clin. Invest., 39:1131.