CHRONIC LIVER DISEASE IN KUALA LUMPUR, MALAYSIA : A CLINICAL STUDY

M V Kudva, M M Zawawi

ABSTRACT

This study was undertaken to analyse the clinical spectrum of chronic liver disease (cirrhosis, and others with portal hypertension) in Kuala Lumpur. Eighty patients were diagnosed over a 6-year period. Twenty-two had biopsy proven cirrhosis while 58 others had portal hypertension with clinical and biochemical evidence of chronic liver disease. The commonest aetiology was alcohol (36%), followed by the idiopathic variety and hepatitis B. The male to female ratio was 4.4:1. Indians had a high prevalence of alcohol-associated chronic liver disease. Overall, ascites was the commonest presentation. Eight patients presented with hepatocellular carcinoma. Spontaneous bacterial peritonitis was diagnosed in 13% of patients undergoing abdominal paracentesis. Gallstones were detected in 37% of patients who underwent ultrasonography. Diabetes mellitus and peptic ulcer disease were noted in 22% and 31% of patients respectively.

Keywords : Chronic liver disease, cirrhosis, alcohol, hepatitis B, spontaneous bacterial peritonitis.

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INTRODUCTION

There have been few reports on the epidemiology and clinical presentation of chronic liver disease in Malaysia. We undertook this study to review the spectrum of liver cirrhosis, and chronic liver disease with portal hypertension seen at a University Hospital in Kuala Lumpur. Factors known to cause chronic liver disease are prevalent in Malaysia. 5-10% of the Malaysian population are hepatitis B carriers [1]. Another factor, alcohol consumption, is reported to be rapidly rising in South East Asia [2].

The objectives of this study were, firstly, to study the aetiology of chronic liver disease in Kuala Lumpur, secondly to determine whether any sex, age or ethnic differences exist between the different aetiological types, and thirdly, to study the clinical presentation of these patients.

MATERIALS AND METHODS

We did a retrospective study on patients with chronic liver disease (cirrhosis, and others with portal hypertension) seen at the Department of Medicine, Faculty of Medicine, National University of Malaysia (NUM) Kuala Lumpur, over a 6-year period (October 1982 to September 1988). Only patients aged 12 years and above were included. Patients were either admitted to the University Medical Unit, General Hospital, Kuala Lumpur, or seen as outpatients at the University Medical Specialist Clinic.

The chronic liver disease group consisted of patients with :

(1) liver cirrhosis diagnosed by liver biopsy

(2) chronic liver disease with portal hypertension, diagnosis of which was based on the following criteria.

Oesophageal varices on endoscopy or characteristic changes of portal hypertension on ultrasonography together with the presence of any one of the three following features:

(1) hypoalbuminemia (serum albumin <30 g/l with reversal of the albumin:globulin ratio and persistent elevation of the prothrombin time (>2.5 sec above control) not correctable with parenteral vitamin K.

(2) presence of significant spider naev (>5) with or without other stigmata; palmar erythema, clubbing, gynaecomastia.leukonychia, loss of pubic or axillary hair.

(3) one or more episodes of hepatic encephalopathy.

Supportive evidence of chronic liver disease included consistent ultrasonographic or 99mT_c radionuclide liver scan features. Ultrasonographic: coarse echogenic liver pattern, with patent and dilated portal and splenic vein, and splenomegaly [3]. Liver scan: decreased and patchy liver uptake with increased splenic and bone marrow uptake [4].

The following parameters were studied in all patients: age, race, sex, presenting symptoms, alcohol

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consumption, history of diabetes mellitus or cholecystectomy, physical signs at first presentation to our unit (stigmata of chronic liver disease, jaundice, palpable liver or spleen, ascites), liver profile (globulin, albumin, bilirubin, ALT, AST, alkaline phosphatase), haematological profile (haemoglobin, TWBC, platelet), prothrombin time and hepatitis B surface antigen (HBsAg) by radioimmunoassay.

Other parameters studied (ie. only in patients in whom these investigation were done), included alphafetoprotein (by immunoelectrophoresis), random blood sugar, serum iron, total iron binding capacity, serum ceruloplasmin, blood and urine copper levels, antinuclear factor (ANF), antimitochondrial antibody (AMA), antismooth muscle antibody (ASMA), endoscopy (for oesophageal varices), ultrasonography of the upper abdomen, radionuclide liver scan and liver biopsy. The findings of diagnostic abdominal paracentesis were also noted.

The following aspects of chronic liver disease were then studied:

(1) *Aetiology of chronic liver disease by race, sex and mean age*

Alcohol-associated chronic liver disease was that occurring in patients with significant alcohol consumption. The latter was defined as almost daily consumption of at least 50 gms of alcohol (equivalent to 2 regular bottles of beer) for a period longer than 8 years [5].

Hepatitis B associated chronic liver disease was that occurring in patients with positive HBsAg.

Idiopathic chronic liver disease included those with negative HBsAg and absence of history of significant alcohol consumption or other secondary causes.

Secondary causes included Wilson's disease, autoimmune chronic active hepatitis, primary biliary cirrhosis and haemachromatosis.

The sex and racial composition of chronic liver disease patients was compared to that of a control population. The latter consisted of all patients seen at the Department of Medicine, Faculty of Medicine, NUM, in 1987. It was assumed that no significant differences existed in the sex and racial composition of the control population, with that of patients seen in the department in the other years of the study. Chi square with Yates' correction when necessary was used to compare the two populations. Odds ratio was calculated in the usual way. An odds ratio indicates the frequency of chronic liver disease associated with alcohol or hepatitis B in one race relative to another. An odds ratio of 1.0 indicates an equal risk; an odds ratio of 3.0 indicates a threefold increase in risk.

Age was defined as the age of onset of the presenting symptom.

(2) *Presenting Symptom*

This was the initial mode of presentation.

(3) *Physical signs and Complications*

This included the signs that were elicited when the patient initially presented to our unit. The frequency of signs and complications within the three aetiological groups (alcohol, hepatitis B, idiopathic) were compared. Hepatocellular carcinoma was diagnosed either on liver biopsy or in the presence of compatible ultrasonographic findings and positive alpha-fetoprotein. Spontaneous bacterial peritonitis was diagnosed on a positive culture of the peritoneal fluid, in a patient with ascites and absence of any obvious intra-abdominal source. Pancytopenia was defined as haemoglobin < 12gm% (male), < 9gm% (female),TWBC 4,000 cu mm, platelet < 80,000 cu mm in the absence of anaemia or leukopenia.

(4) *Associated diseases*

Diabetes mellitus was defined as the presence of either (1) a positive history of diabetes mellitus in patients on regular follow-up and treatment (oral hypoglycemics or diet) or (2) a Fasting Blood glucose >7.8 mmol/L, and 2 hour post prandial blood glucose >11.0 mmol/L on admission.

Gallstones was defined as the presence of either (1) gallstones seen on ultrasonography in our unit or (2) a history of cholecystectomy for gallstones within the preceeding 6 years. The prevalence of gallstones was calculated as the number of patients with gallstones as a percentage of all those who underwent ultrasonography or had a recent history of cholecystectomy.

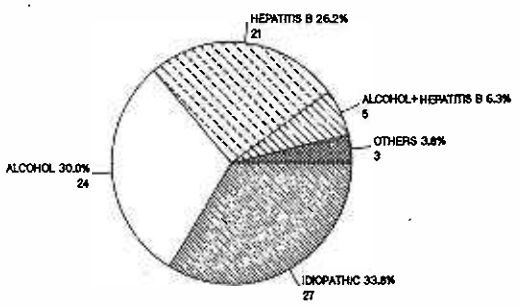
Peptic ulcer (PU) disease was diagnosed in the presence of either (1) endoscopic evidence of PU or (2) a history of surgery for PU.

RESULTS

Eighty patients had chronic liver disease. Chronic liver disease was biopsy proven to be due to cirrhosis in 22 patients.

In the other 58 patients, the diagnosis was based on the presence of portal hypertension (56 had oesophageal varices on endoscopy while 2 had consistent ultrasonographic features) with clinical and/or biochemical evidence of chronic liver disease. In 53 out of these 58 patients the diagnosis of chronic liver disease was further supported by characteristic ultrasonographic and/or radionuclide liver scan features. Liver biopsy was contraindicated in the majority of patients, due to prolongation of prothrombin time (not correctable by vitamin K) and/or thrombocytopenia.

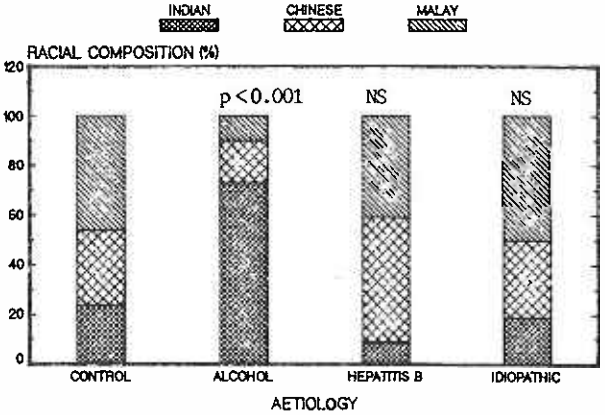
Fig 1
Aetiology Of Chronic Liver Disease
(HBsAg not done in patients with alcohol history)



(1) Aetiology of chronic liver disease by sex, age and race (Fig 1, 2)

Alcohol-associated chronic liver disease was the commonest, occurring in 36% (29 patients) followed by the idiopathic type (34%) and hepatitis B (33%). Five patients with alcohol-associated chronic liver disease were HBsAg positive. The mean duration of alcohol consumption was 22 years (Range: 8-42 years). Investigations to exclude Wilson's disease was done in those aged below 30 years.

Fig 2
Racial Composition of Control Population and Chronic Liver Disease (Alcohol, Hepatitis B, Idiopathic).



Other races (3 Indonesians, 2 Orang Asli) were excluded

Odds Ratio (95% confidence interval)
NS-Not significant.
Alcohol Indian vs Non-Indian 8.39 (3.52-20.58) p < 0.001,
Chinese vs Non-Chinese 0.50 (0.16-1.36) NS,
Malay vs Non-Malay 0.13 (0.03 - 0.26) p < 0.001.
Hepatitis B Chinese vs Non-Chinese 2.37 (0.96 - 5.8) NS,
Malay vs Non-Malay 0.80 (0.31-1.99) NS,
Indian vs Non-Indian 0.32 (0.06-1.41) NS.

There was a significant difference in the male: female ratio of chronic liver disease patients compared to the control population (4.4 and 1.1 respectively). Alcohol associated liver disease had the highest ratio of 13.5. Hepatitis B and idiopathic liver disease had lower ratios of 3.5 and 2.9 respectively.

The mean age of all patients was 52 years. Hepatitis B patients had the lowest mean age of 45.6 years (Range 23-66 years). Both the alcohol and idiopathic liver disease patients had higher mean ages of 53.6 (30-76) and 56.7 (5-80) years respectively.

Indians had a significantly higher prevalence of chronic liver disease associated with alcohol. Odds ratio: Indians vs Non-Indians 8.39, Chinese vs Non-Chinese 0.50, Malays vs Non Malays 0.13. Chinese appeared to have a higher (though not reaching statistical significance) prevalence of hepatitis B associated chronic liver disease. Odds ratio : Chinese vs Non-Chinese 2.37, Malays vs Non-Malays 0.80, and Indians vs Non-Indians 0.32. There was no difference in the racial composition of patients with idiopathic chronic liver disease.

A 62-year old Chinese man had autoimmune chronic active hepatitis based on liver biopsy, negative HBsAg and positive ASMA. Primary biliary cirrhosis was diagnosed on liver biopsy in a 54-year old Malay lady with a 15-year history of jaundice and pruritus. She had a normal endoscopic retrograde cholangio-pancreaticogram with positive AMA. Wilson's disease, in a 15 year old Malay boy was based on bilateral Kayser-Fleischer rings, low serum ceruloplasmin levels, negative HBsAg and absence of autoantibodies.

(2) *Presenting Symptom (Table I)*

Abdominal distension due to ascites, and ankle oedema were the commonest presentations. Four were noted to have stigmata of chronic liver disease during examination for unrelated symptoms. In two patients with pancytopenia, the diagnosis of chronic liver disease was delayed by more than a year. The patient with intestinal pseudo-obstruction had ascites; extensive investigations failed to reveal a cause and the obstruction resolved on conservative treatment. One patient had peritonitis; laporotomy showed bleeding from the gastro-hepatic ligament secondary to a hepatoma.

Table I
Presenting Symptoms in Chronic Liver Disease

Symptom	%
Ascites/Ankle Oedema	53
Jaundice	23
Gastrointestinal bleeding	20
Upper abdominal pain only	7
Hepatic encephalopathy	5
Bleeding (other than gastrointestinal)*	5
Stigmata of chronic liver disease - incidental finding	5
Pancytopenia	4
+ Others	4

* Bleeding gums - 2, Epistaxis - 1, Menorrhagia - 1.
\+ peritonitis - 1, Intestinal pseudo-obstruction-1, Hepatosplenomegaly alone - 1

Table II
Presenting Physical Signs and Complications in Chronic Liver Disease

Signs/ Compli-cations	Alcohol %	HBsAg %	Idiopathic %	All patients %
Ascites	72	71	78	73
Stigmata of chronic liver diseases	69	57	60	64
Hepatomegaly+	55	38	30	45
Splenomegaly+	17	57	30	45
Jaundice	41	48	26	18
Pancytopenia++	3	24	26	18
Thrombocytopenia++	28	33	15	25
Hepatocellular carcinoma	7	29	7	10
Spontaneous* bacterial peritonitis	-	-	-	13

\+ In 3 patients [alcohol group (1), hepatitis B (1) idiopathic (1)] it was not possible to palpate for hepatomegaly/splenomegaly because of ascites.
++ In one alcohol related cirrhotic, the haematological profile was not done
* Spontaneous bacterial peritonitis was diagnosed in 4 out of 30 patients who had abdominal paracentesis.

(3) *Physical Signs and Complications (Table II)*

Hepatocellular carcinoma was noted in 8 patients. The mean age was 57 years (Range : 23-75). Two were biopsy proven. The remaining six had positive alpha-fetoprotein with compatible ultrasonographic changes. Six out of the 8 were HBsAg positive, including two with histories of significant alcohol consumption.

Spontaneous bacterial peritonitis was diagnosed in 4 out of 35 patients who underwent paracentesis. The indication for paracentesis was recent clinical decompensation. Two had fever with abdominal

Table III
Associated Diseases

	Chronic liver disease	Malaysian Population [16,22]
	%	%
Gallstones	37*	11.8 - 13.7
Diabetes mellitus	22	3.9 (Malays) 4.9 (Chinese) 16.0 (Indians)
Peptic ulcer	31	

* Gallstones were detected in 17 out of 97 patients who underwent ultrasonography

tenderness, whilst the others were afebrile and had no abdominal signs. Organisms cultured were Klebsiella (2 cases), E. Coli (1) and Bacillus species (1). Tuberculous peritonitis was diagnosed on laparoscopic biopsy in an alcoholic, who presented with fever and a tender doughy abdomen.

(4) *Associated Diseases (Table III)*

Eighteen patients (23%) had a history of diabetes mellitus. In the majority, the diabetes was controlled by diet and oral hypoglycemics. None required insulin therapy.

Gallstones were detected in 17 out of 47 patients (37%) who underwent ultrasonography. An additional two patients had a recent history of cholecystectomy, giving a total of 41%. Peptic ulcer disease was noted in 31% of the patients (including 3 patients with a history of gastrectomies for peptic ulcer). The ratio of gastric to duodenal ulcer was 2:1.

DISCUSSION

Chronic liver disease associated with alcohol was the commonest. We defined significant alcohol consumption as the minimum amount of alcohol needed to cause a statistically significant increase in the incidence of cirrhosis in a well nourished population. Pequignot [5] has shown that the minimum 'cirrhogenic dose' is 40 gm in men and 20gm in women.

There was a male preponderance of chronic liver disease especially alcoholic. The male to female sex ratio in alcohol related liver disease in the West ranges from 2 to 10: 1 [6,7]. In our series it was even higher at 13.5:1. Similarly, hepatitis B related chronic liver disease was more frequent in males. The proportion of male carriers is substantially greater then females. This predominance has been explained by postulating cross-reactivity between HBsAg and a male determined tissue antigen [8] so that the male is tolerant of HBsAg and therefore has an impaired immune defence against it.

The mean age of our chronic liver disease patients (52 years) was similar to that noted by Ross in Penang [9]. Hepatitis B associated chronic liver disease occurred at a younger age (45.6 years) compared with the alcohol related type (53.6 years). Studies elsewhere have shown that the age of onset of symptoms in hepatitis B chronic liver disease is about 42 years [10], whereas for alcoholic cirrhosis it is 50 years [11].

Indians appeared to have a significantly increased frequency of alcohol associated chronic liver disease with an odds ratio of 8.39. Similar findings have been noted by Ross [9] in Penang, and Chong [12] in Singapore. Alcohol is emerging as a major problem in South East Asia; in Malaysia, alcoholism appears to occur chiefly among Indians [2].

Hepatitis B associated chronic liver disease was the commonest cause in Chinese with an odds ratio of 2.37. Malays and Indians had lower prevalence rates. This finding corresponds with the carrier rate of hepatitis B amongst Chinese, Malays and Indian blood donors [1].

About a third of our patients did not have a recognisable cause. There were no racial differences in this group. Non-A, Non-B hepatitis (NANB) has been implicated as a possible aetiological agent.

Chronic liver disease is reported in 0-50% of persons (median 20%) who have sporadic NANB hepatitis [13]. This presents as chronic persistent hepatitis, chronic active hepatitis or cirrhosis.

Almost three quarters of our patients presented with decompensation, particularly ascites. The frequency with which patients presented with jaundice and gastrointestinal bleeding was similar to that in other series, with ranges from 10 to 25% [6]. The clinician should be aware of unusual presentations (bleeding gums, epistaxis, menorrhagia, pancytopenia), as the diagnosis of chronic liver disease in these instances was sometimes missed for months.

Hepatomegaly is commoner in alcoholic cirrhosis, whereas splenomegaly is present significantly more often in hepatitis B related cirrhosis [6]. Similar findings were noted in our series. Pancytopenia was presumably due to hypersplenism; hence the increased frequency of pancytopenia in hepatitis B and idiopathic chronic liver disease. Splenectomy is not recommended for the hypersplenism of cirrhosis, unless the patient is actually suffering from leucopenia or thrombocytopenia. Only one of our patients underwent splenectomy for this indication. The circulating platelets and leukocytes, although in short supply are in contrast to those in leukemia, functioning well.

Spontaneous bacterial peritonitis (SBP) is defined as an infection of pre-existing ascites in the absence of any obvious intra-abdominal source. All the four patients with SBP presented with recent decompensation. The prevalence of SBP in chronic liver disease has been reported to be between 8 and 18% [14]. In one third of patients, there was no fever or signs directly referrable to the abdomen [16]. Hence the need to have a high index of suspicion in any chronic liver disease patient with ascites and recent decompensation. The majority of the SBPs are due to gram negative bacili as was the case in our study [15].

Gallstones were detected in 37% of our patients who underwent ultrasonography compared to an incidence of 11% in an asymptomatic Malaysian population [16]. The majority of our patients were asymptomatic, with gallstones being diagnosed during routine ultrasonography. In a survey of autopsy records, gallstones were found in 29% of the cirrhotic patients (irrespective of the type) and 13% of the non-cirrhotic population [17,18]. Pigment gallstones account for the increase. This increase does not seem to be related to lithogenic (low cholesterol holding) bile [19]. The increase in pigment gallstones could be related to an increased

secretion of bile pigments in bile [20] . Because of the increase in complications associated with cholecystectomy in cirrhotics [21], biliary tract surgery should only be reserved for symptomatic cirrhotics in whom other non-surgical approaches cannot be used (eg. endoscopic papillotomy).

The prevalence of diabetes mellitus in our series was 22% compared to a prevalence of between 3.9% and 16.4% in the Malaysian population [22]. There is a well known association between diabetes mellitus and chronic liver disease [23]. The reported prevalence of diabetes in chronic liver disease varies greatly, partly due to the use of different criteria for diagnosis. Studies have suggested that diabetes occurs in 17% of cases, although in Saudi Arabia the figure approaches 40% [24]. Cirrhotics are twice as likely as the general population to have diabetes [25]. Factors predisposing to diabetes in cirrhotics include peripheral insulin resistance and hyperglucagonemia [23,24].

Peptic ulcer is said to be common in cirrhosis but information on the comparative frequency of peptic ulcer in the general population is not easy to obtain, and this association has been questioned [25]. If the incidence is increased in cirrhosis the reason for it is not obvious. In our series 31% had a history of peptic ulcer as compared to a prevalence of 21% in a series of patients presenting at a local endoscopy unit [26].

CONCLUSION

There were ethnic and sex differences in the prevalence of the different aetiological types of chronic liver disease. Alcohol-associated chronic liver disease was commoner in Indians while the hepatitis B associated type was the commonest type in the Chinese. Public health measures to reduce alcohol abuse and the hepatitis B carrier state would be expected to reduce the incidence of chronic liver disease.

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