THE SPECTRUM OF LIVER DISEASE IN PENANG: A CLINICAL AND HISTOLOGICAL STUDY

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SUMMARY

We analysed clinical and histological diagnoses in patients admitted with liver-related illnesses in order to determine the spectrum of liver disease in our community. In a total of 380 such patients, liver disease was sixfold more frequent in males than in females. Admissions for cirrhosis were more common amongst the Indian ethnic group. Indians constituted 39% of the admissions (expected 11.7%), Chinese 37% (expected 51%) and Malays 21% (expected 36%) ($\leqslant 2$ = 293, p = H 0.001). Liver histology from 179 of the patients was reviewed blind by one pathologist. Based on the histological findings, the pre-biopsy diagnosis was 'wrong' in 75% of cases.

The age standardized incidence rate of hepatocellular carcinoma was 22/100,000/year in males and 5/100,000/year in females. However, the peak age of onset was in the seventh decade and the age specific incidence in males aged 60 years or older was 93/100,000/year. The ethnic group representation of patients with hepatocellular carcinoma did not show a racial preponderance.

This study highlights a public health problem related to acute viral hepatitis and alcohol abuse. It also confirms a high incidence of hepatocellular carcinoma.

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INTRODUCTION

In our state, liver disease accounts for upto 3% of admissions to medical wards and is the seventeenth commonest cause of death.[1] Government statistics show that cirrhosis of liver is more frequent in males compared to females (3.3:1) whilst 40% of deaths due to cirrhosis occur within the Indian ethnic group, who comprise only 10% of the population.[2] Factors known to cause chronic liver disease, such as hepatitis B virus infection, are prevalent in Malaysia,[3] but the nature of the liver disease is not well described.

The objectives of this study were, firstly, to define the spectrum of liver disease occurring in our community: secondly, to determine any differences in incidence of disease between the three main ethnic groups and thirdly, to calculate the minimum incidence of hepatocellular carcinoma.

PATIENTS AND METHODS

The Penang General Hospital serves an estimated 290,486 persons. Based on admission data, 51% of this population are Chinese, 36% Malays, 11.7% Indians and 1.3% other ethnic groups. We analysed adult medical admissions (10 years or older) for suspected liver disease over a 35-month period from August 1980. A record was made of each patient's identity, sex, ethnic origin and diagnosis on discharge. The patients were grouped under one of four main diagnostic categories, namely acute viral hepatitis, cirrhosis, hepatocellular carcinoma and liver abcess. This data was used to determine the male to female sex ratio and the ethnic group representation amongst patients with liver disease.

During the same period of time, 179 patients had successful liver biopsies performed either by percutaneous needle aspiration, laparoscopy or laparotomy. The liver biopsy material was examined blind by one pathologist and was classified according to nine categories (Table 1). The liver biopsies of a random sample of 50 patients were stained using the orcein method to detect the proportion of patients with hepatitis B surface antigen present.[4] A sample of 90 patients who were biopsied were examined in detail to assess the correlation between the pre- and post-biopsy diagnoses.

Over a 38-month period from January 1981, patients were identified who had either biopsy-positive hepatocellular carcinoma or alpha-feto-protein positivity in association with a clinical diagnosis of hepatocellular carcinoma, but no liver biopsy.

Alpha-feroprotein measurement was performed by immuno-electrophoresis. This data was used to estimate the minimum incidence rate of hepatocellular carcinoma in our community. The minimum incidence was defined as the number of histologically diagnosed or alpha-feroprotein positive cases of hepatocellular carcinoma observed during a set period divided by the number of persons alive during that period.[5]

The minimum incidence was used to derive age-specific and age-standardized (standardized to a European population) incidence rates.[6]

During the same period hepatitis B surface antigen was tested for by a reversed passive haemagglutination technique (Cellognost, Behring Institute, Germany) in 260 individuals with acute viral hepatitis and 115 patients with suspected chronic liver disease.

A sample of 196 in-patients were interviewed to obtain information on the prevalence of alcohol consumption in our community. In addition, data were collected on the number of alcohol-related admissions to the medical wards.

Basic demographic data about the population served by the Penang General Hospital was obtained from the Population and Housing Census of Malaysia 1980,[7] Vital Statistics Peninsular Malaysia 1979[2] and the Department of Medical Health and Dentistry, Pulau Pinang.

Statistical analysis was performed using the Chi Square test, with Yates's correction for four-fold tables and the U-test of Wilcoxon, Mann and Whitney.

Addendum

Calculation of age-specific incidences: of all the in-patient admissions to public and private hospitals in Pulau Pinang, 30.4% are admitted to Penang General Hospital. Hence, it is estimated that out of a total population of 955,545 in Penang, Penang General Hospital serves 290,486 persons.

Example 1: Calculation of age specific incidence of hepatocellular carcinoma in males > 59 years.

Calculation	Basis
290,486/2 = 145,243 males	male: female ratio 1 : 1.
5.6% of 145,243 = 8134	5.6% of males in that age group.
(24/38) x 12 = 7.6	24 males with HCC in that age group identified in 30 months, hence 7.6/yr.
(100,000 x 7.6)/8134 = 93/100,000 / year	

Example 2: Calculation of age specific incidence in Chinese males > 59 years.

Calculation	Basis
51% of 8134 = 4148	51% of admissions are Chinese; 4148 Chinese males in that age group.
(16/38) x 12 = 51	16 Chinese males identified with HCC in 38 months, hence 5.1/year.
(100,000 x 5.1)/4148 = 123/100,000/year	

RESULTS

A total of 380 patients with suspected liver disease were admitted to medical wards during the study period. These individuals constituted 3% of male medical admissions and 1.1% of female admissions. Of these patients, 380 were classified into one of the above diagnostic categories, the remainder had jaundice or hepatomegaly that was not clearly delineated as being due to a primary liver disease. The ratio of males to females in the 380 patients was 6:1 compared to 1.6:1 for 20,040 patients without liver disease admitted to the same wards (X^2 = 121, $p = < 0.001$).

Figure 1 shows the diagnoses on discharge of these patients. Liver disease was far more frequent in Indians than that expected from the population served by the hospital. In Indians the proportion was 39% (expected 11.7%), in Chinese 37% (expected 51%), in Malays 21% (expected 36%) and in others 3% (expected 1.7%) (X^2 = 293, $p = < 0.001$). This disparity was mainly due to a greater number of cases of cirrhosis amongst both Indian males and females and acute viral hepatitis amongst Indian males. Admissions for alcohol-related illness, excluding cirrhosis, was also more frequent amongst Indian males, who comprised 58 of 91 (64%) such admissions (X^2 = 249, $p = < 0.001$) (Fig. 2).

Liver biopsy was performed on approximately 70% of eligible patients, based on the criteria that biopsy could be indicated in patients with a pre-biopsy diagnosis of hepatocellular carcinoma, cirrhosis, hepatomegaly or jaundice. The histological diagnoses of the 179 patients are given in Table 1.

Miscellaneous diagnoses included lymphoma and leukaemia infiltrates, hamartoma of the liver, cholangitis, fatty change, tuberculosis and chronic venous congestion. Necrosis included patients with viral hepatitis and drug hepatitis. In particular, there was one rare case of D-penicillamine-associated cholestasis with centrizonal necrosis.

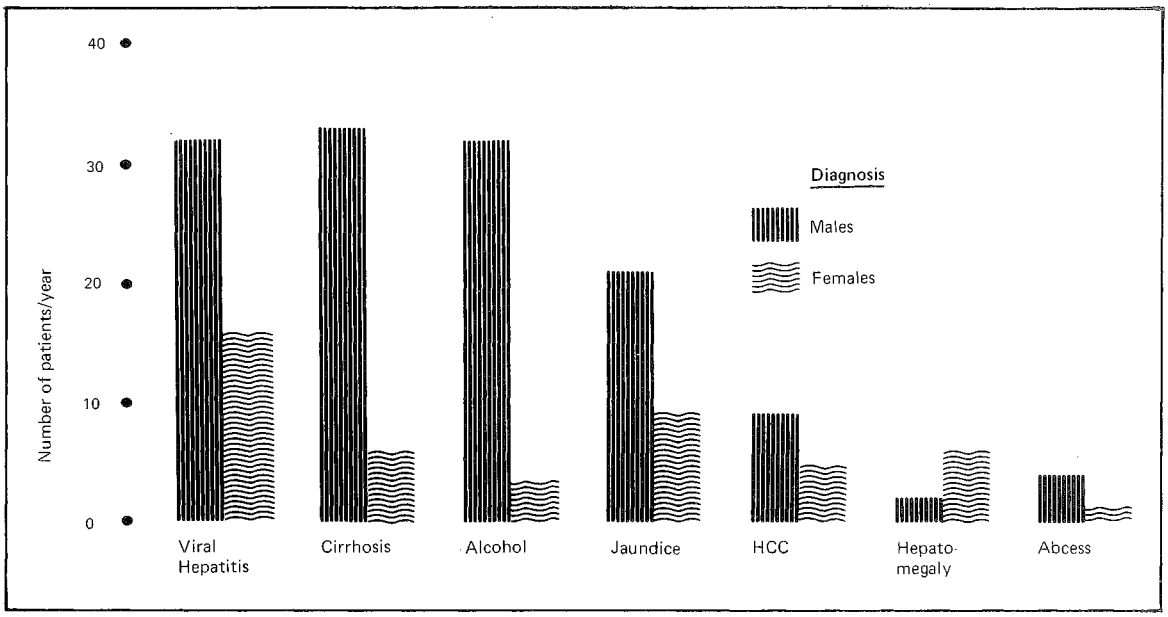

Fig. 1 Diagnosis on discharge in patients with liver disease, expressed as the mean number of patients seen per year. Hatched bars represent males and crosshatched bars represent females. HCC indicates hepatocellular carcinoma, the male to female ratio was 6:1 ($X^2 = 85$ $p = < 0.001$).

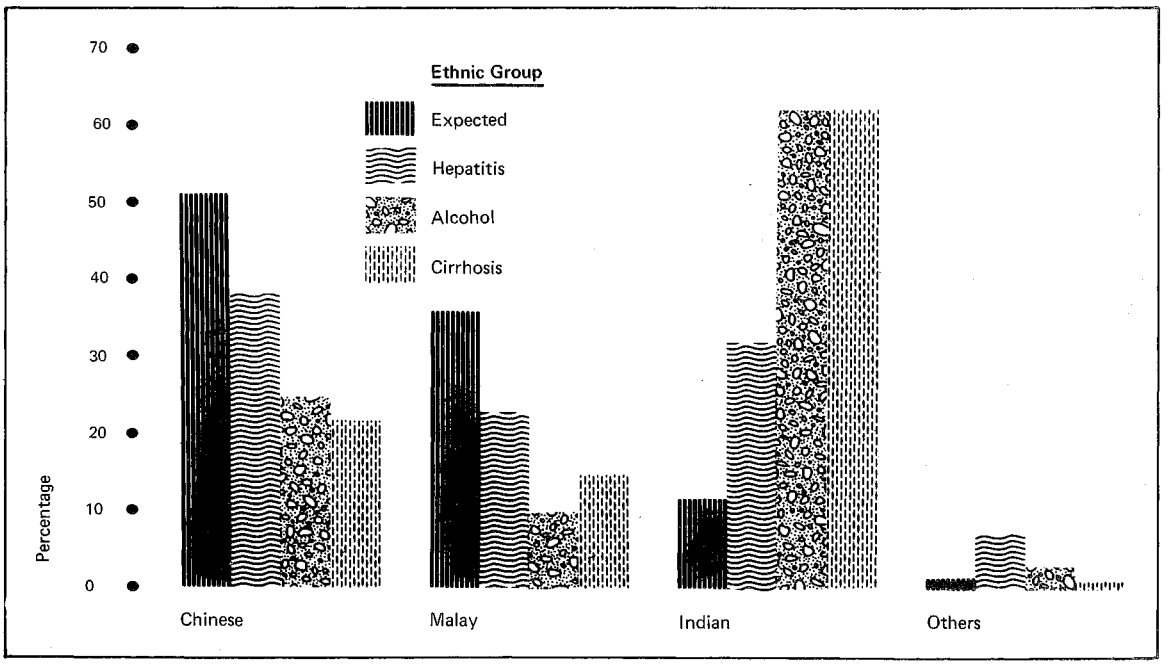

Fig. 2 Ethnic representation in 380 males admitted because of acute viral hepatitis, cirrhosis or alcohol-related illnesses. There were significantly more Indian patients with these three diagnoses than expected from the ethnic group proportions in the population served by the General Hospital, Penang ($X^2 = 445$ $p = < 0.001$).

TABLE I

HISTOLOGICAL DIAGNOSIS BASED ON LIVER BIOPSY IN 179 PATIENTS

Diagnosis	Number of Patients*	
Miscellaneous	40	
Normal	35	
Cirrhosis	29	(32)
Hepatocellular carcinoma	23	
Metastases	18	
Necrosis	10	
Chronic active hepatitis	8	(19)
Liver-cell dysplasia	7	(12)
Chronic persistent hepatitis	5	(6)
Liver abscess	4	

*As some patients had more than one histological lesion, the figures in parenthesis represent the total number of patients with that lesion.

TABLE II

MEDIAN AGE, AGE RANGE AND HISTOLOGICAL DIAGNOSIS IN PATIENTS WITH SUSPECTED LIVER DISEASES

Diagnosis	Median Age (Years)	Age Range (Years)
Normal biopsy	51.5	17 – 73
Chronic active hepatitis	50	20 – 80
Cirrhosis	52	42 – 75
Metastases	60	34 – 82
Hepatocellular carcinoma	64	19 – 74

*Patients with hepatocellular carcinoma were significantly older than patients with cirrhosis ($p = > 0.01$).

Of the 32 patients with cirrhosis, 12 (38%) had mixed nodular cirrhosis, nine (28%) macronodular cirrhosis, eight (25%) alcoholic cirrhosis and five (16%) micronodular cirrhosis. Cirrhosis when present with chronic active hepatitis was usually of the mixed nodular type. Cirrhosis and chronic active hepatitis were commonest in the 50-to-60-year age group, whilst hepatocellular carcinoma and metastatic infiltration were most common a decade later ($p = < 0.01$)(Table II). There was positive orcein staining indicative of hepatitis B surface antigen in only 10% of the liver biopsies tested. Hepatitis B surface antigen was present in the serum of 53 (20%) individuals with acute viral hepatitis and 15 (13%) of those with chronic liver disease.

There were 35 cases of biopsy-proven hepatocellular carcinoma and an additional 17 patients with a positive serum alpha-fetoprotein, but no liver biopsy proof. The incidence increased with age such that in males aged 60 years or older the incidence was 93/100,000/year, and 23/100,000/year in females. The age specific incidence/100,000/year (>14 years) was, in Chinese males 16, in Malays 18, and in Indians and others 6. The ethnic group frequency of hepatocellular carcinoma was the same as that expected from that parent population ($X^2 = 3.6$, $p = > 0.05$).

The age standardised incidence/100,000/year was in males 22 and in females 5, the male to female sex ratio was 4:1.

There was poor correlation between the clinical diagnosis and the biopsy diagnosis. In 61 (75%) of 81 patients a 'wrong' diagnosis was made prior to biopsy. Amongst the 127 male in-patients interviewed, 17 (29%) of 58 Chinese, 9 (26%) of 35 Malays and nine (27%) of 34 Indians admitted to consumption of alcoholic beverages. Only four of 69 female in-patients admitted to alcohol intake.

DISCUSSION

The main finding of this study was a marked disparity between the ethnic groups for the

incidence of liver disease. The increased incidence of cirrhosis in Indians was paralleled by an increase in admissions for both viral hepatitis and alcohol-related illness. If viral hepatitis is a factor connected with this excess of cirrhosis, then it would have to be of the hepatitis B or non-A, non-B virus types, as hepatitis A virus is thought not to be a cause of chronic liver disease. In fact a recent study showed that only 33% of acute virus hepatitis patients in Kuala Lumpur have serological evidence of A virus infection.[5]

We have found that in Pulau Pinang, 40% of patients with acute viral hepatitis have evidence of hepatitis A infection as the cause of their hepatitis, 17% evidence of hepatitis B and 41% evidence of non-A, non-B hepatitis (unpublished observations). As the risk of developing chronic liver disease following hepatitis B and non-A, non-B infections is upto 10% and 40% respectively, acute viral hepatitis must be a major initiator of chronic liver disease in Malaysia.

Another indication that non-A, non-B related chronic liver disease may be prevalent in Malaysia is the finding that only 15% of our patients with chronic liver disease are hepatitis B surface antigen positive, compared to 9% in the blood donor population; whilst only 10% of patients had hepatitis B surface antigen in liver biopsy material.[9]

Alcohol abuse is the other cause for this over-occurrence of cirrhosis, and there is additional evidence of alcohol-related disease in Indians, namely a significantly increased incidence of oesophageal cancer compared to Malays and Chinese (unpublished observations).[10] Oesophageal varices are also significantly more common in our Indian population (unpublished observations).

In contrast the proportion of male in-patients consuming alcoholic drinks was similar in the three ethnic groups, that is a median of 28% of patients. Presumably there must be marked differences in the amount and frequency of alcohol ingestion between the ethnic groups. However there may be a racial predilection towards cirrhosis as there are genetically-determined factors related to histocompatibility antigens that can influence the development of cirrhosis.[11] At the same time it is important to exclude non-alcoholic liver disease occurring in patients with heavy alcohol consumption.[12]

Liver biopsy was essential for accurate diagnosis of liver disease as the pre-biopsy diagnosis was only accurate in 25% of patients. A 'wrong' pre-biopsy diagnosis was usually due to overdiagnosis of hepatocellular carcinoma, when the actual diagnosis was metastases or hepatomegaly without liver disease. This overdiagnosis indicates that few patients with hepatocellular carcinoma, once admitted, would have been missed. However blind biopsy will fail to diagnose 19% of patients with hepatocellular carcinoma, whilst alpha-fetoprotein measurement by immuno-electrophoresis is positive in only 67% of Malaysian patients.[13] As such, the incidence quoted must be considerably less than 'true' incidence.

Nevertheless the age standardised incidence rate of 22/100,000/year in men is 22 times the rate in the United Kingdom,[6] but is only slightly less than the incidence quoted for Singapore of 29/100,000/year.[14] Inclusion of those patients with a positive alpha-fetoprotein, but no confirmatory liver biopsy, in calculating the incidence of hepatocellular carcinoma can be justified by the fact that a false positive result is very infrequent when this test is performed by immunoelectrophoresis.[15]

Hepatocellular carcinoma in Africa and Taiwan occurs in the second to fifth decades,[16] but in our patients and Singaporeans, the incidence was highest in the 50 – 60 year age group. The sex ratio based on the age standardised rates of 4:1 is similar to other countries.[6,16] Haepatocellular carcinoma in the tropics usually occurs on a background of macronodular cirrhosis16 and in our patients was most common about 10 years after the median age for cirrhosis. Currently it is believed to be related to the co-carcinogens aflatoxin and hepatitis B virus,[16] although recently non-A, non-B infecttion has been implicated as a causative factor.[17]

Genetic factors may also be important, as hepatocellular carcinoma in Chinese is associated with the histocompatibility antigens HLA-B5 and B15.[18] We could find no ethnic preference for hepatocellular carcinoma in our survey.

Liver-cell dysplasia was found in 10% and macronodular cirrhosis in 7% of patients with abnormal liver biopsies. Both these conditions are thought to be precursors of hepatocellular carcinoma,[19] in particular the risk of malignancy occurring in Asians with macronodular cirrhosis is as high as 50%.[16]

Screening of such patients might allow earlier diagnosis and surgery, as only 10% of Malaysian patients have a resectable tumour at the time of diagnosis and approximately half of those operated upon are dead within one year.[13]

In conclusion, there is an ethnic group disparity for admissions for cirrhosis of the liver probably related to alcohol and the sequelae of acute viral hepatitis. Public health measures to reduce alcohol abuse and transmission of acute viral hepatitis would reduce both the morbidity and mortality of alcoholic liver disease.[20,21] Regular screening of patients with liver-cell dysplasia and macronodular cirrhosis by serum alpha-fetoprotein measurement and ultrasound, would preempt the development of inoperable hepatocellular carcinoma.[22]

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