THE FREQUENCY OF NON-A, NON-B HEPATITIS IN ACUTE AND CHRONIC LIVER DISEASE

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SUMMARY

Serological markers were used to determine the infective agents causing acute viral hepatitis in 246 patients. The frequencies of the five viral infections investigated were: non-A, non-B hepatitis – 99 patients (40.2%); hepatitis A - 98 patients (39.8%); hepatitis B - 43 patients (17.5%); cytomegalovirus - 4 patients (1.6%); and Epstein-Barr virus – 2 patients (0.8%). The log mean ages of presentation for the three predominant infections were: hepatitis A - 18 years; hepatitis B - 25 years; and non-A, non-B hepatitis – 30 years ($F = 18.8$, $p = < 0.001$). 52% of all cases were Malays (expected 32.7%); 32% Chinese (expected 54.6%); and 16% Indians (expected 11.5%) ($X^2 = 53$, $p = < 0.001$). Hepatitis A virus infection was more common amongst Malays whilst non-A, non-B hepatitis was more frequent amongst Chinese and Indians. 28% of children (< 16 years) and 50% of adults had serological markers of previous hepatitis B infection. The variation in frequency for the different forms of hepatitis amongst the three main ethnic groups would suggest that socio-economic and/or cultural factors are important in the propagation of acute viral hepatitis in Malaysia. HBsAg-negative chronic liver disease in our community may be a product of the high incidence of non-A, non-B hepatitis.

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INTRODUCTION

In the state of Pulau Pinang, acute viral hepatitis is the fifth most common, notifiable infectious disease and the minimum incidence of symptomatic hepatitis is 2 per 1000 per year. Hepatitis B (HBV), but not hepatitis A (HAV), is stated to be associated with chronic liver disease in 5 – 10% of infected individuals.[1] However, we have previously noted that only 13% of Malaysian patients with chronic active hepatitis or cirrhosis are HBsAg-positive.[2] As the sporadic form of non-A, non-B (NANB) infection can cause chronic liver disease in up to 50% of infected patients, we felt it pertinent to assess the frequency of non-A, non-B infection in our population.[3]

MATERIALS AND METHOD

A circular was sent to hospital-based doctors within the state of Pulau Pinang, requesting that they forward blood for hepatitis serological studies from all patients with a diagnosis of recent acute viral hepatitis. During a nine-month period, sera from a serial sample of 246 patients were collected and stored at $-70^{\circ}C$. A record was made of each subject's age, sex, ethnic grouping and referring hospital. The referring hospitals served: A-an area designated metropolitan town. Patients attending the hospital in this area were recorded as 'urban' residents. B - areas designated urban small or rural. Patients seen in hospitals in these areas were recorded as 'rural' residents. In 119 patients, data on serum levels of bilirubin, glutamic pyruvate transaminase (SGPT) and alkaline phosphatase were recorded.

HAV infection was assessed by radio-immunoassay (RIA) of IgM antibody to HAV (HAVAB^{R}-M, Abbott Laboratories, Diagnostic Division, North Chicago, USA). HBV infection was investigated by enzyme-linked immunosorbent assay (ELISA) of HBsAg (Enzygnost^{R}-HBsAg, Behringwerke AG, Marburg, West Germany), and by RIA of Anti-HBs (AUSAB^{R}, Abbott Laboratories) and RIA detection of Anti-HBc (CORAB^{R}, Abbot Laboratories). All patients who had no evidence of HAV infection as the cause of their hepatitis were further investigated for cytomegalovirus and Epstein-Barr virus infections. Cytomegalovirus IgM antibodies were measured by an ELISA technique and a positive reaction at a dilution of 1 in 80 was accepted as evidence of recent infection (Enzygnost^{R} Anti-Cytomegalovirus, Behringwerke AG).

Epstein-Barr virus infection was investigated using an indirect immunofluorescence test for antibodies to Epstein-Barr viral capsid antigen. A positive test at a dilution of 1 in 640 was considered indicative of recent infection.[4] In this study, patients suffering from HBV hepatitis were defined as those positive for HBsAg in the absence of evidence of HAV, cytomegalovirus or Epstein-Barr virus infections. Non-A, non-B hepatitis was presumed if there was no evidence of the latter four infections.

Data were analysed by the Chi square test with Yates's correction for fourfold tables and by one way analysis of variance, following logarithmic transformation.

RESULTS

99 patients (40.2%) had evidence of NANB infection, 98 (39.8%) HAV infection, 43 (17.5%) HBV infection, 4 (1.6%) cytomegalovirus infection and 2 (0.8%) patients Epstein-Barr virus hepatitis. Four cases of NANB and one case of HBV were related to blood transfusion. Four cases of NANB and one case of HBV occurred in known drug addicts. All other cases of acute viral hepatitis were believed to have occurred sporadically.

The age distribution for the three commonest types of viral hepatitis is shown in Fig. 1. The log mean ages of presentation were: for HAV infection, 18 years (2SD range 5 to 69); for HBV infection, 25 years (10 to 64); and for NANB

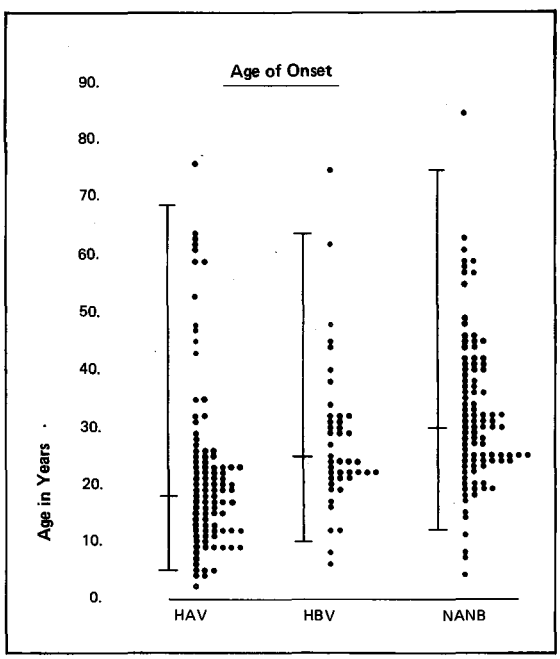

Fig. 1 Age of presentation for HAV, HBV and NANB forms of hepatitis. The bars represent the log mean and two standard deviation range. The ages of onset differed significantly accordingly to the type of hepatitis ($F = 18.8$, $p = <0.001$).

hepatitis, 30 years (12 to 75). These ages of onset differed significantly ($F = 18.8$, $p = < 0.001$).

The frequencies of the three predominant forms of hepatitis amongst males and females are shown in Table I. The male to female sex ratio for hepatitis was 1.9:1 (expected 0.97:1) ($X^2 = 27$, $p = < 0.001$). Although their mean ages are similar, 49% of males but only 31% of females had evidence of previous HBV exposure as assessed by HBsAg, Anti-HBs and/or Anti-HBc positivity ($X^2 = 5.5$, $p = < 0.02$).

There were significantly more Malays with acute viral hepatitis. This ethnic group formed 52% of all cases (expected 32.7%), whilst Chinese formed 32% (expected 54.6%) and Indians formed 16% (expected 11.5%) ($X^2 = 53$, $p = < 0.001$) (Fig. 2). The minimum annual incidences for acute viral hepatitis, based on patients in this survey were: Malays 2.46/1000; Indians 2.30/1000; and Chinese 1.08/1000. This increased incidence of acute viral hepatitis was due to HAV infection. Malays constituted 70% of cases in the metropolitan town area (expected 33%) and 78% of cases of HAV hepatitis outside of this area. There was no difference between urban Malays and rural Malays for the frequencies of the different forms of hepatitis.

There were more cases of HBV and NANB hepatitis in the urban area. The incidence of NANB hepatitis was higher amongst Chinese and Indians compared to Malays in this area

TABLE I

FREQUENCY AMONGST MALES AND FEMALES OF DIFFERENT TYPES OF ACUTE VIRAL HEPATITIS AND OF SEROLOGICAL MARKERS OF PAST HBV INFECTION IN SUBJECTS NOT CLASSIFIED AS HBV HEPATITIS.

EVENT	MALES	FEMALES
All hepatitis	161 (66)	83 (34)
HAV	64 (66)	33 (34)
NANB	57 (58)	41 (42)
HBV	36 (84)	7 (16)
Past HBV infection	59 (73)	22 (27)

Figures in parenthesis represent percentage. In 2 patients the sex was unknown.

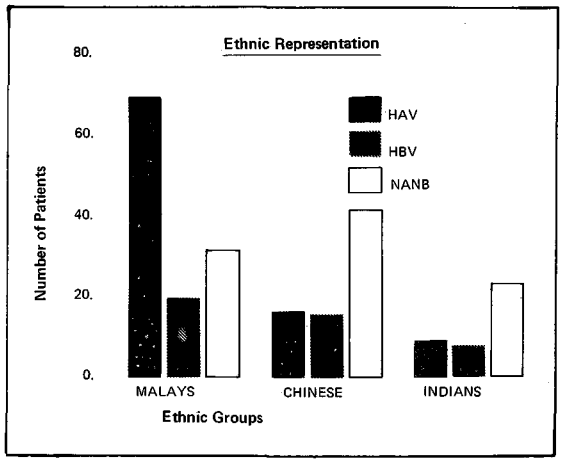

Fig. 2 The number of cases of HAV, HBV and NANB according to ethnic group. There were more cases of hepatitis amongst Malays than amongst the other two ethnic groups ($x^2 = 53$, $p = < 0.001$). This was due to an excess number of HAV cases.

($X^2 = 22$, $p = < 0.001$). The prevalence of HBV hepatitis was similar amongst all three ethnic groups. Regarding previous exposure to HBV, if patients with HBV hepatitis were excluded, then 28% of children (< 16 years) and 50% of adults had already been exposed at the time of the study.

Patients with NANB infection had a less severe biochemical hepatitis than individuals infected with the other viruses (Table II).

DISCUSSION

This study showed a high frequency of NANB hepatitis in our community and a disparity between ethnic groups regarding the types of hepatitis contracted. However, the figures presented here represent mainly cases of icteric hepatitis and as such do not give the true frequency of hepatitis. This is because symptoms like jaundice occur in only approximately 25% of individuals with HBV or NANB infection and 10% of patients with HAV infection.[1,3,5] Furthermore, IgM class Anti-HBc, which can now be used to either discriminate between recent HBV infection and a carrier state, or identify those patients with acute HBV hepatitis who have undetectable HBsAg,[6] was not tested for.

The reason for the age differential between the

three predominant types of hepatitis is not clear, but the same pattern has been described by others.[7-10] HAV infection occurs early in life in Malaysians, so that by the third decade 74% of individuals have been exposed.[8] The lasting immunity that occurs with the acquisition of Anti-HAV prevents further infection later in life.[11] HBV infection also occurs early in life through vertical and horizontal transmission. In our subjects 28% had markers of previous HBV infection by the age of 16 years. In neighbouring Singapore, 37% of children under 12 years of age have had HBV exposure.[12] Once again development of Anti-HBs, Anti-HBc or a carrier state will prevent new infection at an older age.[11]

In contrast, NANB hepatitis peaked in presentation at the age of 30 years. This later age of presentation, compared to HAV and HBV infections, appears to be a characteristic of the sporadic form of NANB hepatitis. In an outbreak of waterborne NANB hepatitis in India, the age of presentation was 20 to 40 years.[13] In both Kuala Lumpur and Sao Paulo, Brazil, the mean age of presentation of NANB hepatitis was 42 years,[8,10] whilst, in Auckland, New Zealand, the mean age was 39 years.[14]

The possible hypotheses for this are: (i) chronic liver disease occurs in up to 60% of individuals with post-transfusion NANB hepatitis and in up to 50% of persons who contract the sporadic form of NANB hepatitis.[3] Symptomatic exacebration of this chronic illness at a later age could mimic acute viral hepatitis; (ii) lack of longlasting immunity would allow repeat infections to occur at any time during life, unlike HAV or HBV infections; (iii) repeated attacks of NANB hepatitis are known to occur in susceptible populations, probably due to continuing exposure and infection with different forms of NANB hepatitis.[11]

The ethnic group disparity could be due to either socio-economic or cultural differences. Possible factors are: (i) choice of eating utensils. HBsAg was demonstrated on 6–50% of household surfaces in a community with a high HBsAg carrier rate.[15] Common eating utensils would serve to propagate transmission of HBV infection and the use of chopsticks and eating from communal dishes may be the cause of the familial clustering of HBV infection seen amongst Chinese. In contrast, Malays and Indians could be more prone to HAV, because of their use of the fingers for eating; (ii) upto 25% of Chinese take traditional, Chinese medicines as well as modern medicine preparations when ill.[16] These traditional cures can be adulterated with corticosteroids and might result in a steroid whitewash effect;[16] (iii) 74% of Malays compared to only 33% of Chinese and Indians are resident in small urban and rural areas and it would seem that the increased likelihood of Malays to develop HAV infection is related to the poorer sanitation found in a rural environment, for example lack of piped water.

Chronic liver disease accounts for upto 3% of

TABLE II

COMPARISON OF LOG MEAN SERUM BILIRUBIN, SGPT AND ALKALINE PHOSPHATASE LEVELS IN THE THREE PREDOMINANT FORMS OF ACUTE VIRAL HEPATITIS

	BILIRUBIN (2-14 μmol/l)	SGPT (5-35 iu/l)	ALK PHOS (15-50 iu/l)
HBV	163 (37-722)	299 (36-2491)	71 (29-173)
HAV	131 (55-309)	204 (12-3413)	77 (41-147)
NANB	100 (15-654)	65 (3-1318)	73 (31-193)
F value	4	12	0.5
	$p = < 0.05$	$p = < 0.001$	not significant

Values in parenthesis are the 2SD range.

admissions to our wards, but we have previously noted that only 15 of 115 (13%) such patients had HBsAg, excluding patients with hepatocellular carcinoma.[2] Alcohol accounts for only 21% of cirrhotic cases. Thus, a large proportion of our patients do not have a recognised agent causing their illness. Chronic liver disease is reported in 0 – 50% of persons (median 20%) who have sporadic NANB hepatitis.[3] This manifests as chronic persistent hepatitis, chronic active hepatitis or cirrhosis, and could account for the disease seen in our HBsAg negative patients.

Finally, hepatocellular carcinoma has been implicated as one of the sequelae of NANB infection. Patients developing this form of cancer are 8 to 10 years older than those with the HBV-related form of hepatocellular carcinoma. They have a history of NANB exposure 13 to 30 years prior to development of the tumour.[3,17] The median age of presentation of hepatocellular carcinoma in Malaysia is 64 years,[2] which differs from the HBV-related form seen in China or Africa, which peaks in the 20 to 40 year age group.[18] Studies need to be done in order to determine whether this older age of onset in Malaysia is due to NANB-induced hepatocellular cancer.

In conclusion, sporadic NANB hepatitis is a common infection in Malaysia and may contribute to the development of chronic liver disease and even hepatocellular carcinoma. Neonatal vaccination with HBV vaccine is necessary, but will only eradicate a small proportion of virus-related liver disease. Identification and elimination of the factors causing the transmission of hepatitis viruses may prove a cheaper alternative to vaccination.

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