PREVALENCE OF HEPATITIS DELTA VIRUS INFECTION IN MALAYSIA

D S K Tan, M Dimitrakakis, S Mangalam, C G Lopez, B G Ooi

SUMMARY

The prevalence of coinfection, superinfection and chronic infection with the hepatitis delta virus (HDV) was studied in 324 hepatitis B surface antigen (HBsAg)-positive Malaysians. Of these, 10.0% (5/50) had coinfection, 5.7% (11/194) had superinfection, but none of the 80 patients with chronic liver disease (CLD) or primary hepatocellular carcinoma (PHC) had chronic infection with HDV. The overall HDV infection was 4.9% (16/324).

One of the coinfection cases acquired the HDV infection as early as 1982. HDV superinfection was detected mainly among IV drug abusers (20% or 7/35) and promiscuous males and females (13.6% or 3/22). They were all asymptomatic. Only 0.8% (1/125) apparently healthy blood donors was infected with HDV. None of the 12 multi-transfused patients examined were positive.

Malaysia is the only Southeast Asian country examined so far in which HDV infection was detected. The reason could be that the IV drug abusers and the sexually promiscuous groups missed being examined in the other countries.

Comparing the HDV infection rates in 4 categories of infected Malaysians (viz. acute hepatitis B patients, IV drug abusers, blood donors and CLD patients) with those of other countries, it was noted that the Malaysian rates were similar to the lowest in the range of prevalence rates of each category in the latter group.

The rate of coinfection in a preliminary study in 1982-84 (9.0% or 1/11) was not very different from that obtained to date (10.0% or 5/50). Although HDV had been introduced into Malaysia at least 5 years ago from an unknown source, it had not spread to the general population but had been restricted to the high risk groups of IV drug abusers and the sexually promiscuous. Close monitoring and attempts to contain or remove the reservoir from these two groups should be made through immunisation with the HBV vaccine and health education.

A study of the frequency of fulminant hepatitis in Malaysia is needed in relationship to both coinfection and superinfection, as there is no valid reason why fulminant hepatitis should occur with superinfection but not with coinfection.

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INTRODUCTION

In 1977, Dr. M. Rizzetto in Italy discovered, by direct immunofluorescence, an agent in the hepatocyte nuclei of patients suffering from chronic HBV infection (1). He found it to be a defective agent which depended on HBV infection for its expression and replication and named it the delta agent or hepatitis delta virus (HDV). Later, it was reported that hepatitis B surface antigen (HBsAg) carriers infected with HDV were likely to suffer from fulminant hepatitis and/or chronic progressive hepatitis.

HDV infection was most commonly found in HBV endemic areas such as Southern Europe (especially South Italy), the Mediterranean countries, the Middle East and some Pacific Islands (2). It is common in people in contact with blood or blood products e.g. intravenous (IV) drug abusers and haemophiliacs. It has not been detected in any of the Southeast Asian countries except for Malaysia (3).

There are 3 situations in which HDV can infect (4):

(a) As a coinfection, in which HDV and hepatitis B virus (HBV) infect a person simultaneously from the same source, causing acute viral hepatitis. The HBV infection usually resolves and resolution of the delta infection necessary follows. This is the usual pattern when drug abusers from communities with a low prevalence of HBV are infected with HDV.

(b) As a superinfection in which HDV causes an attack of acute hepatitis in a chronic HBV carrier. Fulminant hepatitis may occur in this situation and carries a high mortality rate. The way to differentiate the two is by detecting, in the cases with coinfection, anti-HBc IgM which is absent in cases with super-infection.

(c) As a chronic infection of an HBV carrier, insidiously causing a progressive chronic active hepatitis. This is more likely to be severe than chronic hepatitis due to

Institute for Medical Research
50588 Kuala Lumpur
Malaysia

D S K Tan, MBBS, DTM & H
S Mangalam, MBBS, M Sc
B G Ooi, OIMHLT

Fairfield Hospital
Melbourne
Australia

M Dimitrakakis

National Blood Transfusion Service
General Hospital
Kuala Lumpur
Malaysia

C G Lopez, DCP, FRCPA

Correspondence to: Dr Tan

HBV alone.

The purpose of this study is to determine the prevalence of HDV infection in Malaysia in the above 3 forms and to pin-point where the main reservoir of infection exists. A comparison of the local situation with those in other countries was also made.

MATERIALS AND METHODS

Sera of 324 HBsAg carriers were tested for delta markers. Of these, 50 were patients classified as suffering from acute HBV infection based on the presence of anti-HBc IgM in their sera and abnormally high serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The remaining 274 were chronic HBsAg carriers of various categories (Table 1).

HBsAg was detected by the reverse passive haemagglutination (RPHA) test using the commercial kit Serodia HBsAg supplied by the Fujirebio Incorporation, Tokyo, Japan. Eleven sera of patients with acute hepatitis B (leptospirosis-negative cases), collected in 1982-1984 and stored at -20°C prior to testing, were examined for anti-HBc IgM by the microtitre solid phase radioimmunoassay (SPRIA) technique. The remaining 39 sera obtained in 1986-1987 were tested for the anti-HBc IgM by the enzyme immunoassay using commercial kits Cozyme M (Abbott Laboratories, Chicago, Ill., U.S.A.).

The detection of delta antigen and antibody in sera was carried out by a microtitre solid phase radio-immunoassay (SPRIA) technique.

The AST and ALT activities were determined according to the methods recommended by the International Federation Clinical Chemistry (5).

RESULTS

The prevalence of hepatitis delta virus infection in Malaysia is summarised in Table I. Five (10.0%) of 50 of the patients with acute hepatitis B had coinfection with HDV, one of whom acquired the infection as early as 1982. Three were positive for HD antigen and two for anti-HD. Of the 5 patients, 3 (60.0%) were Malay and two (40.0%) Indian, their ages ranging from 17 to 35 years (Table 2).

Of 194 chronic HBsAg carriers, 11 (5.7%) had superinfection with HDV and were positive for anti-HD (Table 1). All were asymptomatic and had no past history of acute hepatitis. No delta markers were found in the 80 patients with chronic liver disease (CLD) or primary hepatocellular carcinoma (PHC).

The highest rate of delta markers was encountered in IV drug abusers (20.0% or 7/35). Five (71.4%) were Malay, one was Chinese (4.3%) and one was Indian (4.3%). They were between 27 and 54 years old. In the promiscuous male and female group, 13.6% (3/22) were positive for anti-HD. Only 0.8% (1/125) of apparently healthy blood donors had HDV infection. None of the 12 multi-transfused HBsAg carriers, comprising haemophilics, thalassaemics and others were positive.

The overall HDV coinfection, superinfection and chronic infection rate was 4.9% (16/124).

Table 1.
PREVALENCE OF HEPATITIS DELTA INFECTION IN MALAYSIA

GROUP	NO. TESTED	DELTA MARKERS (%)
COINFECTION	50	5 (10.0)
SUPERINFECTION	194	11 (5.7)
IV drug abusers	35	7 (20.0)
Prostitutes	6	1(16.7)
Male homosexuals	16	2 (12.5)
Blood donors	125	1 (0.8)
Multitransfused patients	12	0
CHRONIC INFECTION		
CLD/PHC	80	0

CLD = Chronic Liver Disease
PHC = Primary Hepatocellular carcinoma

Table 2.
PARTICULARS OF THE 5 ACUTE HEPATITIS B PATIENTS* WITH HDV COINFECTION

PATIENT	AGE	SEX	RACE	ANTI-HBcIgM	HD-Ag	ANTI-HD
(1)	26	MALE	INDIAN	+	+	–
(2)	29	MALE	MALAY	+	+	–
(3)	35	MALE	MALAY	+	+	–
(4)	17	MALE	MALAY	+	–	+
(5)	22	MALE	INDIAN	+	–	+

* NON DRUG ADDICTS

DISCUSSION AND CONCLUSION

HDV infection is common in the general population in countries highly endemic for hepatitis B such as the Mediterranean basin, parts of Africa, the Middle East and parts of South America, where transmission tends to occur by person-to-person contact (6). In the western world, where hepatitis B is not endemic, HDV infection appears to be largely restricted to IV drug abusers and their close contacts (7, 8).

It would be expected, therefore, that Malaysia and her surrounding countries, being highly endemic for hepatitis B, would also be endemic for HDV infection and that delta markers would be easily detected in the general "normal" population. This was not so, however, as shown by Dimitrakakis et al (9) who reported that delta infection was either not detected or rare in some highly hepatitis B-endemic countries like the Philippines, Singapore, Taiwan, Japan, China and Vietnam (Table 4). The reason for this paradox is not clear.

Table 3.
PARTICULARS OF THE 11 HBsAG CHRONIC CARRIERS WITH HDV SUPERINFECTION

GROUP	PATIENT	AGE	SEX	RACE	HD-AG	ANTI-HD
IV DRUG ABUSER	(1)	31	M	MALAY	-	+
	(2)	34	M	MALAY	-	+
	(3)	31	M	MALAY	-	+
	(4)	54	M	CHINESE	-	+
	(5)	27	M	MALAY	-	+
	(6)	33	M	INDIAN	-	+
	(7)	36	M	MALAY	-	+
HOMOSEXUAL	(1)	30	M	MALAY	-	+
	(2)	23	M	CHINESE	-	+
PROSTITUTE	(1)	21	F	CHINESE	-	+
BLOOD DONOR	(1)	22	M	CHINESE	-	+

Table 4.
PREVALENCE OF HDV INFECTION IN CHRONIC CARRIERS OF HBsAG IN SOME ASIAN COUNTRIES

COUNTRY	NO. EXAM	DELTA MARKERS (%)	REFERENCE
JAPAN	152	1.3	2
TAIWAN	53	7.5	2
PHILIPPINES	146	0	8
SINGAPORE	245	0	8
VIETNAM	473	2.2	8
CHINA	43	0	8

Table 5.
DELTA MARKERS IN 4 CATEGORIES OF HBsAG CARRIERS IN MALAYSIA COMPARED WITH OTHER COUNTRIES

CATEGORY	MALAYSIA (%)	OTHER COUNTRIES (%)[10]
ACUTE HEPATITIS B	10.0 (n = 50)	11-44 (n = 112-1, 050)
IV DRUG ABUSERS	20.0 (n = 35)	19-81 (n = 8-181)
BLOOD DONORS	0.8	0-0.7 (n = 33-250)
CHRONIC LIVER DISEASE	0 (n = 80)	1-66 (n = 11-871)

It would appear, therefore, that absence of delta markers among "healthy" carrier population cannot be used as evidence that infection with the delta agent is uncommon in that community, at least not for Asian countries. In Malaysia, delta hepatitis tends to be associated with parenteral and sexual modes of transmission rather than by person-to-person or casual contact. For some obscure reason, HDV infection is not as highly transmissable as HBV infection in this area. Perhaps the prevalence of HDV infection in the other Asian countries might be similar to that of Malaysia, if drug abusers and homosexuals/prostitutes were tested in these areas.

Comparing the HDV infection rates in 4 categories of infected Malaysians (viz. acute hepatitis B patients, IV drug abusers, blood donors and CLD patients) with those of other countries, it may be noted that the Malaysian rates were similar to the lowest rates of each category in the latter group (Table 5) (10).The rate in the 22 Malaysian promiscuous male and female subjects (13.6%) occupies intermediate position between that of the acute hepatitis B patients (10.0%) and the IV drug abusers (20.0%). Unfortunately, data from other countries for this group were not available for comparison. No HDV infection was detected in the 12 multitransfused patients. Such people are usually highly susceptible to infection with HDV and a rate of about 50% has been reported (11).

It is interesting but puzzling to note that delta markers were very uncommon among the many HBsAg carriers with chronic liver disease (CLD) or primary hepatocellular carcinoma (PHC) in Asian countries (9). Although 80 Malaysian HBsAg carriers with CLD/PHC were examined, none was positive for delta markers. These findings confirm those of Chen et al (12) and Govindarajan et al (13) who found low prevalence of delta infection among patients with CLD or PHC in Taiwan. In Italy, the prevalence of anti-delta in carriers with CLD is 24.6% (14). Follow-up studies of some cases with HDV super infection showed that within a period of 2 to 6 years after infection, the patient developed severe liver damage (15).

Delta antigenaemia is transient occurring early in acute delta infection and HD antigen is soon replaced by the antibody. Three of the 5 Malaysian cases with coinfection had HD antigen which was not detected at all in any of the cases with superinfection. One of the cases with HD antigen had acute hepatitis as early as 1982. It is not known whether he belonged to any high risk group. At that time, the preliminary study (done in 1981-84) gave a HDV prevalence rate of 9% (1/11) which is comparable with the present accumulated rate of 10.0% (5/50) obtained with the extended study continued from 1986-87. This means that HDV had been introduced into Malaysia at least 5 years ago from an unknown source, but had fortunately not spread to the general population and had been confined to two high risk groups as far as it is known. The overall rate of HDV infection in Malaysia so far is about 5.0%. This needs to be closely and regularly monitored. The reservoir in these groups needs to be contained if possibly by means of immunisation with HBV vaccine and health education.

The occurrence of fulminant hepatitis in Malaysia is not known although one gets the impression from casual enquiry that it is not common. This needs to be studied in depth in relationship to both coinfection and superinfection with HDV as there is no valid reason why fulminant hepatitis should occur with superinfection but not with coinfection.

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