Hepatitis C virus infection in chronic liver disease in Natal

P. N. Soni, D. R. Tait, W. Gopaul, M. A. Sathar, A. E. Simjee

The aim of this cross-sectional seroprevalence study was to determine the prevalence of antibodies to hepatitis C virus (HCV) (anti-HCV) in patients with cirrhosis, hepatocellular carcinoma (HCC) and chronic active hepatitis (CAH) attending a referral hospital in a hepatitis B virus (HBV)-endemic area in South Africa. One hundred and ten patients with suspected cirrhosis, 44 with suspected HCC and 6 with chronic hepatitis were initially included. The diagnoses were confirmed in 77 patients with cirrhosis (histologically or macroscopically at

Gastrointestinal Unit and Departments of Medicine and Medical Virology, University of Natal and King Edward VIII Hospital, Durban

P. N. Soni, F.C.P. (S.A.), M.MED.

D. R. Tait, M.MED. (PATH.) (VIROL.)

W. Gopaul, DIP. MED. TECH. (VIROL.)

M. A. Sathar, M.MED. SCI.

A. E. Simjee, F.R.C.P.

peritoneoscopy), 33 patients with HCC (histologically or elevated alpha-fetoprotein levels plus focal lesion on hepatic imaging) and 6 patients with CAH (histologically) without antinuclear antibodies. All patients were tested for anti-HCV with the Abbott second-generation enzyme immunoassay combined with a supplemental neutralisation assay, and hepatitis B surface antigen (HBsAg). Anti-HCV seroprevalence for cirrhosis, HCC and CAH were 18/77 (23%), 8/33 (24%) and 2/6 (33%) respectively. HBsAg was detected in serum in 16 (21%), 15 (46%) and 1 (17%) patient respectively. Only 1 patient (with cirrhosis) was positive for both anti-HCV and HBsAg. Of those who were anti-HCV-positive, 4/18 (22.2%) cirrhotics, none with HCC and 1/2 (50%) with CAH, had previously received blood transfusions, resulting in a cumulative frequency of 5/28 (18%). Our results indicate that HCV is an important aetiological agent in the pathogenesis of chronic liver disease in our patients. In the majority of patients (82%), the infection was not transfusion-related. Thus, screening of blood donors for anti-HCV would not prevent the majority of cases of chronic liver disease secondary to HCV. It appears as if HCV and HBV have different modes of transmission in southern Africa.

S Afr Med J 1996; **86:** 80-83.

Hepatitis C virus (HCV) has been proven to be the major cause of transfusion-associated and sporadic non-A, non-B hepatitis in the world. Since the development of a recombinant protein-based assay for the detection of antibody to this virus,[1] rapid progress has been made and sensitive and specific markers of HCV infection are now available. Studies show that the addition of anti-HCV testing to blood donor screening has improved the safety of therapy with blood and blood products.[2-4]

The worldwide carrier rate for hepatitis C in blood donors is 0.3 - 1.5%;[5] this amounts to about 500 million. There is now convincing evidence of the slow sequential progression from acute HCV-related non-A, non-B hepatitis through chronic hepatitis and cirrhosis to hepatocellular carcinoma (HCC).[6] The disease may be mild or slowly progressive. Approximately 50% of patients infected with HCV develop biochemical evidence of chronic hepatitis, and approximately 20% of those with chronic hepatitis have histological evidence of cirrhosis.[7]

The role of hepatitis B virus (HBV) in the development of chronic liver disease and HCC is well known.[8] It has been estimated that there are at least 2 million HBV carriers in South Africa, and HCC associated with chronic HBV infection is a major cause of death among black men.[9] Cirrhosis is common in the black population in Natal and is the eighth most common disease encountered at King Edward VIII Hospital, the major referral hospital for KwaZulu/Natal.[10] To evaluate the importance and role of HCV in chronic liver disease at this hospital we screened patients with confirmed cirrhosis, chronic active hepatitis (CAH) and HCC.

Patients and methods

Between March 1991 and February 1992, patients with suspected chronic liver disease seen at King Edward VIII Hospital were screened. One hundred and ten patients had suspected hepatic cirrhosis and the diagnosis was confirmed in 77. Sixty patients had histologically proven disease, with fibrosis and nodule formation; in the remaining 17 the liver was visualised peritoneoscopically, and a macroscopic diagnosis of cirrhosis was made. In these 17 patients, histological confirmation could not be obtained because of either the fragmented nature of the biopsy specimen or the presence of a coagulopathy or thrombocytopenia.

Forty-four patients with suspected HCC were seen, and the diagnosis was confirmed in 33. The diagnosis was histological in 20 patients, and the remaining 13 had markedly elevated serum alpha-fetoprotein levels together with a focal lesion on hepatic imaging. Six patients with CAH were evaluated; all had histologically proven CAH with elevated aminotransferase concentrations and an absence of antinuclear antibodies. All patients were questioned about previous blood transfusion.

A commercially available second-generation enzyme immunoassay (EIA) kit was used to test serum specimens (Abbott Laboratories, Chicago, Ill., USA). The kit was used according to the manufacturer's instructions and repeatedly reactive specimens were tested by a supplemental assay for validation with Abbott HCV neutralisation EIA. Specimens which neutralised were considered to be true positives; all other specimens were regarded as false positives. All patients also had their sera tested for hepatitis B surface antigen (HBsAg) by radio-immunoassay (Ausria-II, Abbott Laboratories, North Chicago, USA). Alpha-fetoprotein levels in the HCC group were measured by radio-immunoassay (Amersham, UK). Ethical approval was obtained from the Ethics and Professional Standards Subcommittee of the University of Natal.

Results

The mean ages of patients in the cirrhosis, HCC and CAH groups were 48 years (range 12 - 85 years), 45 years (range 12 - 71 years) and 40 years (range 17 - 65 years) respectively. Male-to-female ratios in these 3 groups were 1.57:1, 2.7:1 and 0.5:1 respectively. Eighteen of 77 patients with cirrhosis, 8/33 with HCC and 2/6 with CAH tested positive for anti-HCV by EIA and the neutralisation test (Table I); this gave a seroprevalence of 23.4%, 24.2% and 33.3% respectively. The seroprevalence for HBsAg in the 3 groups tested was 20.8% (16/77), 45.5% (15/33) and 16.7% (1/6) respectively.

Table I. Prevalence of anti-HCV* and HBsAg in patients with cirrhosis, HCC and CAH

	Anti-HCV +		HBsAg +	
Group	No.	%	No.	%
Cirrhosis (*N* = 77)	18	23.4	15	20.8
HCC (*N* = 33)	8	24.2	15	45.5
CAH (*N* = 6)	2	33.3	1	16.7

*Abbott-II with neutralisation EIA.

Of all patients in all the groups, only 1 patient in the cirrhosis group tested positive for both anti-HCV and HBsAg. In patients who tested positive for anti-HCV, a history of blood transfusion prior to the onset of the liver disease was present in 4 (22%) patients with cirrhosis, none with HCC and 1 (50%) with CAH; this gave a cumulative frequency of 18% (5/28). The mean age of patients in the cirrhosis group who were HBsAg-positive was 43 years compared with 59 years for those who were anti-HCV-positive. Comparative ages for the HCC group were 32 years for those who were HBsAg-positive and 59 years for those anti-HCV-positive. Analysis of only those patients who were HBsAg-negative gave an anti-HCV prevalence of 29.5% for the cirrhosis group ($N = 61$) and 44.4% for the HCC group ($N = 18$).

Discussion

Since the identification of the HCV genome and the availability of a specific antibody test, data on HCV infection have accumulated rapidly, but almost all information is from developed countries. In a recent study, we reported the seroprevalence of anti-HCV antibodies (Ortho-II) in 35 685 volunteer blood donors to be 0.16%, 0.22%, 0.34%, and 0.75% in whites, coloureds (mixed origin), Asians and blacks respectively in KwaZulu/Natal.[11]

It has been shown that about 90% of individuals with antibody to HCV have an infectious virus in their blood.[3] This indicates that our patients with chronic liver disease who were anti-HCV-positive are likely carriers of the virus, and that there is probably a strong association between the virus and the liver disease. This would make HCV an important aetiological agent in the pathogenesis of chronic liver disease in our patients, in addition to HBV and alcohol.[12]

The 23% seroprevalence of anti-HCV in our patients with cirrhosis was lower than figures reported from Spain (55.6%),[13] in HBsAg-negative patients from Taiwan (43%)[14] or in patients from elsewhere in Africa (51%).[15] The seroprevalence for patients with HCC (24%) was similar to that reported by Kew *et al.*[16] in southern African blacks,[1] from Mozambique (36.6%),[17] from the more northern areas of Africa (Tunisia and Senegal) (37%)[15] and Taiwan (33%).[14] Other studies from the Far East have reported higher prevalences of HCV than HBV in HCC patients.[6,18] However, our prevalence is much lower than reports on HCC from Spain (75%)[13] and Italy (65%).[19] One of the major difficulties in comparing results of earlier serological tests by means of first-generation assays with more recent data is the lack of sensitivity and specificity of the former. Second-generation tests with supplemental confirmatory assays have now been shown to be far superior.[20]

In only 18% (5/28) of our patients was there a history of previous blood transfusion. Therefore, in the remaining 82% the infection was sporadically transmitted or community-acquired by modes of transmission which are as yet unclear. This is in contrast to most studies from Western countries where the use of blood products and parenteral drug use account for approximately 50% of cases.[21] In Taiwan, one-third to one-half of the anti-HCV-positive patients with cirrhosis or HCC had received blood transfusions 10 - 30 years before diagnosis.[14] However, since chronic hepatitis occurs so long after blood transfusion, it is possible that some patients in our study may not have recalled their transfusion many years ago. Also, retrospective studies indicate that up to 60% of patients who are transfused die within 2 years from the underlying conditions that necessitated the transfusion.[22] It has been shown that there is no difference in the outcome of acute post-transfusion and sporadic non-A, non-B hepatitis secondary to HCV,[23] and that the post-transfusion and sporadic types are due to the same agent.[24]

That 1 patient demonstrated both HBsAg and anti-HCV antibodies suggests that co-infection with the two viruses is uncommon and that HCV appears to be more important in HBsAg-negative chronic liver disease. This is contrary to the finding of Bruix *et al.*[13] who found a 50% prevalence of anti-HCV among Spanish patients with HBsAg-positive HCC, which suggested that cancer may occur because of a combined oncogenic action of both viruses, at least in some cases. Previous evidence indicates that patients infected with more than one virus are likely to develop more serious liver disease than those infected with a single agent.[25] Co-infection does not appear to be a feature in our patients. This suggests that the two viruses may not share a common mode of transmission.

The difference in the mean ages of HBsAg-positive and anti-HCV-positive patients in the cirrhosis (43 years v. 59 years) and HCC groups (32 years v. 59 years) suggests that HCV may be acquired later in life than HBV. A similar difference in mean age has also been shown in other studies.[26,14,18] Alternatively, it may be that the HCV runs a more protracted and indolent course and that patients therefore present much later in life. If HCV is acquired later in life, this would support the theory that its mode of transmission differs from that of HBV, which is known to spread horizontally in early childhood in southern African blacks.[27,28] Another possibility is that the local HCV strain is different from the strains detected in Western countries; this therefore resulted in a different mode of spread; different subtypes of HCV genomes have been described in Japan.[29]

In conclusion, this study demonstrates that HCV plays a significant role in the aetiology of chronic liver disease in our patients. HBV remains the major aetiological agent for the development of HCC in southern Africa, though the prevalences of HBV and HCV in cirrhotics were similar. Transmission via blood and blood products is uncommon; screening of blood donors would therefore not prevent the majority of cases of chronic liver disease secondary to HCV. Further studies are needed to determine the exact modes of transmission of HCV, which appear to be different from those of HBV.

We are grateful to Mr M. Naicker and Mr T. Madlala for assistance with data collection, and the Medical Superintendent, Dr A. M. Seedat, for permission to perform this study. This study was supported by a grant from the University of Natal Research Fund.

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Accepted 3 Aug 1993.