The majority of hepatitis B carriers are not on regular surveillance in Singapore

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ABSTRACT

Introduction: Carriers of hepatitis B virus (HBV) are at risk of developing long-term complications. Regular surveillance helps detect treatable chronic hepatitis, cirrhosis and liver cancer, and is recommended by practice guidelines in the United States, Europe and Singapore. However, there have been few studies evaluating the follow-up of HBV carriers. This study seeks to determine the proportion of HBV carriers on regular follow-up in Singapore and the impact on hepatitis B disease.

Methods: An advertisement was taken in local newspapers advertising for free screening to HBV carriers. 387 persons answered the advertisement. The screening comprised history-taking, physical examination, blood tests (liver panel, alpha-foetoprotein, hepatitis B surface antigen (Ag) and hepatitis B eAg) and ultrasonography of liver. Further evaluation was conducted if the screening results were abnormal.

Results: Of the 387 HBV carriers, 346 (89 percent) were male and 375 (97 percent) were Chinese. Their mean age was 39 years (range 20-60 years) and 36 percent were positive for HBeAg. 247 (64 percent) were not on regular screening over the past 12 months. 19 (5.4 percent) patients were diagnosed to have complications, namely: 13 had HBeAg-positive chronic hepatitis, two had HBeAg-negative chronic hepatitis, one had early liver cancer who recovered well after a curative resection and three had compensated cirrhosis.

Conclusion: Our screening programme diagnosed 5.4 percent of complications among 387 asymptomatic HBV carriers. However, 64 percent of the study subjects were not screened regularly and may pose an important public health threat if they develop long-term complications. Further studies are needed to evaluate and improve patient compliance for screening.

Keywords: chronic hepatitis B, hepatitis, hepatocellular carcinoma

Singapore Med J 2004 Vol 45(9):423-426

INTRODUCTION

Hepatitis B virus (HBV) infection is an important local and global health problem. More than 350 million individuals are chronically infected worldwide, and 4.1% of Singaporeans are carriers of HBV[1,2]. During the course of HBV infection, an estimated 15% to 40% of patients would develop complications including acute exacerbations, liver cirrhosis and hepatocellular carcinoma (HCC)[3]. Hence, it was not surprising that liver cirrhosis and liver failure were the ninth most common cause of death in Singapore and HCC was the fourth most common cancer among Singaporean males[4]. As HCC could develop in hepatitis B carriers in the absence of cirrhosis, an effective cancer surveillance strategy must include both cirrhotic and pre-cirrhotic patients, that is, asymptomatic carriers, in the screened population[5]. Hepatitis B carriers are also at risk of developing acute exacerbation, which is potentially fatal[6]. Hence, regular surveillance for chronic hepatitis, acute exacerbations or development of HCC among HBV carriers is needed to ensure early detection of such complications and their timely treatment.

In 2003, the guidelines of the Ministry of Health in Singapore recommended regular surveillance for complications among carriers of hepatitis B be performed every six to 12 months[7]. Such a nationwide surveillance programme would only be successful and effective if compliance with the programme among hepatitis B carriers is high. However, it is unclear what proportion of hepatitis B carriers are on regular follow-up, as this will have a bearing on the success of a hepatitis B surveillance programme. In this study, we assessed the proportion of hepatitis B carriers who were on a regular surveillance programme and the impact on hepatitis B outcomes.

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Table I. Subjects with various diagnostic endpoints.

Variable	Patients on regular screening (n=140)	Patients not on regular screening (n=247)	Total (n=387)
Abnormal LFT	23 (16.4%)	26 (10.5%)	49 (12.7%)
Chronic hepatitis	7 (5%)	8 (3.2%)	15 (3.9%)
Cirrhosis	1 (0.7%)	2 (0.8%)	3 (0.8%)
HCC	1 (0.7%)	0	1 (0.3%)

HCC: hepatocellular carcinoma, LFT: liver function test

METHODS

An advertisement was placed in local newspapers for a free once-only screening panel of tests for hepatitis B carriers. Subjects who were known hepatitis B carriers were invited to take part in this programme. HBV carrier status of all subjects was re-confirmed by testing of HBsAg. Blood tests and ultrasonography were performed at our institution. Subjects were then scheduled for clinic appointments with a hepatologist for overall assessment and clinical advice. Triphasic computed tomography (CT) of the abdomen and follow-up appointments were arranged when alpha-foetoprotein (AFP) level was elevated, or when focal lesion was detected on ultrasonography. This study was approved by the Institutional Review Board of our hospital.

The screening panel comprised ultrasonography of the hepatobiliary system, liver panel, AFP level, HBsAg, HBeAg and quantitative HBV deoxyribonuclear acid (DNA) assay (detection range 10^2 to 10^8 copies/mL; Cobas Amplicor, Roche Diagnostics, Pleasanton, CA, USA). All subjects were also reviewed and examined by a hepatologist. Chronic hepatitis B (CHB) was defined as elevation of alanine transferase (ALT) >1.5 times upper limit of normal with HBV DNA level $>10^5$ copies/mL, and was further divided into HBeAg-positive CHB and HBeAg-negative CHB, depending on the status of HBeAg[6]. Histology was required for the diagnosis of cirrhosis or HCC. Subjects with screening performed within the last 12 months were considered to have prior screening.

Data were analysed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). Continuous and categorical variables were compared by Student's t test or chi-square test as appropriate. A value of $p<0.05$ was considered statistically significant.

RESULTS

Three hundred and eighty-seven HBsAg carriers were screened consecutively over a period of four months. All were well with no symptoms or known complications of CHB. The age of the subjects was 39.4 (±0.4) years and 346 (89%) were male. Three hundred and seventy-five (97%) subjects were Chinese, nine (2%) were Malay and three (1%) were of other races. One hundred and forty subjects (36%) were positive for HBeAg. Two hundred (52%) subjects had positive family history of hepatitis B, 124 (32%) had no known family history and 63 (16%) were not sure. One hundred and forty (36%) subjects had seen their personal doctors for surveillance over the last 12 months, while the other 247 (64%) did not. Between subjects who were and were not on surveillance, no difference was noted in family history of hepatitis B, age, race and gender.

Serum bilirubin was 10.6 (±0.3) μM (normal <30μM), ALT 50 (±3) U/L (normal <70 U/L), aspartate transferases (AST) 32 (±1) U/L (normal <50 U/L), alkaline phosphatase (ALP) 74 (±1) U/L (normal <140 U/L), AFP 4.9 (±0.7) μg/L (normal <15μg/L). Forty-nine (13%) subjects had elevated ALT, of which 15 (3.9%) had CHB. Thirteen (3%) had HBeAg-positive CHB and two (0.5%) had HBeAg-negative CHB. The characteristics of subjects in different diagnostic endpoints are shown in Table I.

Among the ultrasonographical findings, 147 (38%) subjects had increased echogenicity consistent with fatty infiltration. Nineteen subjects were found to have ultrasonographical parenchymal features (increased echogenecity with irregular surface) suggestive of liver cirrhosis, but none agreed to liver biopsy. Among them, three were subsequently found to have platelet counts $<140 \times 10^6/mm^3$ and were considered to have probable cirrhosis, but none had evidence of decompensation such as jaundice or ascites on ultrasound studies.

Five subjects had focal lesion on ultrasonography of the liver, but only one had elevated AFP at 44μg/L. He was a 32-year-old man who, unfortunately, refused to undergo triphasic CT and remained well after one year. Another subject was a 28-year-old man who had normal AFP level and a subcentimetre lesion that appeared benign on ultrasonography; he was followed-up and showed no evidence of

having HCC. Three other subjects had triphasic CT, which were normal with no enhancing lesion seen.

Nine subjects had elevated AFP (>15μg/L) and one was found to have HCC on CT. He was a 54-year-old man with no previous symptoms, such as abdominal discomfort or weight loss. His AFP was elevated at 253μg/L and his abdominal ultrasonographical studies showed increased echogenicity consistent with fatty infiltration, but subsequent CT showed a 2cm enhancing lesion in the left lobe. He underwent left hepatectomy with curative intent and the histology revealed a 1.8cm HCC with underlying cirrhosis. His post-operative course was complicated by HBV acute exacerbation, which responded to lamivudine subsequently. None of the other eight subjects had any evidence of HCC.

Among the 15 subjects with CHB, four agreed to undergo liver biopsy for further evaluation, which showed active hepatitis with fibrosis in three and cirrhosis in one patient. Two of them took part in an antiviral therapeutic trial, in which subjects were given lamivudine with or without therapeutic HBV vaccines, while the other two opted for open-labelled lamivudine treatment. The other 11 subjects were unwilling to undergo liver biopsy or treatment for active hepatitis.

DISCUSSION

In this study, we found that 57 (14.7%) subjects had abnormal screening results (47 with elevated liver enzymes, five with nodule on ultrasonography of the liver and nine with elevated AFP levels) that warranted further evaluation. Complications of HBV infection were found in 19 (5.4%) screened subjects (15 with chronic hepatitis, three with probable compensated cirrhosis and one with HCC). Our results showed that screening for asymptomatic HBV carriers is effective in diagnosing early complications. Although no difference was found between patients who have regular screening and those that do not, this may be due to the small sample size. As only 5.4% of patients were found to have complications, a much larger sample size would be needed to detect differences between those who have regular screening and those that do not. Nonetheless, potent and effective antiviral agents are now available in suppressing viral replications. Hence, it can be postulated that when these 5% of the patients with complications are treated promptly, risk of progression in them could be retarded or even reversed[8].

On the other hand, antiviral therapy can only be successfully utilised if patients needing treatment are diagnosed and treated. In our study, an alarming 64% of participants had not had screening over the last 12 months. As there were an estimated 120,000 hepatitis B carriers in Singapore, this would translate to more than 75,000 hepatitis B carriers not being screened regularly[2]. Based on an estimated rate of 2% developing decompensation and HCC annually[9], that would result in 1,500 patients developing end-stage liver cirrhosis and HCC annually in Singapore. A study in the United States estimated the mean cost of such hospitalisation for a patient with cirrhosis was US$14,063[10]. In our hospital, the mean cost for complications of HBV were S$5,094 for liver cancer, S$8,870 for variceal bleed, S$3,343 for decompensated cirrhosis, and S$100,480 for liver transplant. Their mean durations of stay were 7.3 days, 8.8 days, 4.1 days and 33 days, respectively. The cost of non-compliance for follow-up translates into an exponential increase in healthcare costs, as end-stage liver disease and advanced HCC consume considerable healthcare resources.

In this study, all subjects were screened by liver panel, AFP and abdominal ultrasonography, which cost S$216 (US$120) per subject. Hence, cost per one treatable HCC diagnosed in our program was S$83,592 (US$46,440) and cost per one subject diagnosed with chronic hepatitis was S$5,573 (US$3,096). These costs, however, did not take into account indirect costs incurred by the subjects, as well as fees for consultation and extra investigations. Further cost-analysis studies should be performed to assess the cost-effectiveness of screening among carriers of chronic hepatitis B.

The poor compliance rate from our study was not surprising. In one 16-year follow-up study on hepatitis B screening in 1,487 patients in Alaska in the USA, approximately 70% of patients had only 1 AFP measurement and <50% had 2 measurements[11]. Unfortunately, no study had evaluated factors that predict non-compliance. Hence, it is uncertain if the current public health policy, through public education and opportunistic screening, is effective.

Although 64% of our subjects are not on regular follow-up, they are sufficiently motivated to respond to the advertisement, and it is possible that the cost of screening could have been a deterrent for regular screening visits. It is likely that the true proportion of hepatitis B carriers who are not on follow-up will be higher, keeping in mind that there may be many patients who are unaware of their hepatitis B status, since hepatitis B is usually asymptomatic. It is unclear why so many hepatitis B carriers are not on regular follow-up. One may speculate that lack of knowledge on hepatitis B, costs of screening and fear of results are factors that play a role. It would be critical to determine such factors since the impact of absence

of follow-up would be realised in terms of increased morbidity and mortality for the individual, and overall higher healthcare costs for the nation. In this era of health prevention and promotion, a positive hepatitis B status must be seen as a cue for action, both on the part of patients and doctors.

We acknowledge limitations of our study. Firstly, we only tested the HBsAg status of our subjects once. Patients with resolving acute hepatitis B may have been included in the study population. However, we believe this would be rare, as we only included subjects with known carrier status of HBsAg and all subjects were asymptomatic. Secondly, using purely elevated ALT and positive HBV DNA, without liver biopsy, as definition for chronic hepatitis B may have over-classified patients who had concomitant liver disease and inactive hepatitis B. While chronic hepatitis C and metabolic liver diseases are rare locally, non-alcoholic fatty liver disease (NAFLD) is prevalent in Western countries and its prevalence is believed to be up to 13% even in the Asian population[12]. Further histology studies on the role of NAFLD and hepatitis B are needed to improve understanding of the interaction. Lastly, we defined chronic hepatitis based on one reading of elevated ALT level, which may have over-classified some patients who normalise their ALT level spontaneously over short-term follow-up. While such patients need not be treated with antiviral agents, they would still benefit from a closer follow-up.

In conclusion, we found that 14.7% of screened subjects had abnormal screening results that warranted further evaluation. Complications of HBV infection were subsequently diagnosed in 5.4% of the screened subjects in this programme. Nearly two-thirds of our subjects with HBV had not been on any surveillance programme over the last 12 months and that posed an important public health issue. Further studies that evaluate patient compliance in HBV surveillance programmes are needed.

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