

Chronic hepatitis B infection in Malaysians

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Abstract

Chronic hepatitis B virus (HBV) infection constitutes a major public health problem particularly in developing countries in East Asia, South-East Asia, the Pacific Basin and Africa. In Malaysia, a developing nation in the South East Asian region, the chronic HBV carrier rate varies between <1% to about 10% depending on the ethnic group studied. The highest frequency is seen among the Chinese, followed by the Malays and lastly the Indians, with a male preponderance of between 2:1 and 3:1. Exposure to the virus among the adult population is estimated to be about 15%, 26% and 36% among the Indians, Malays and Chinese respectively. Serological study of adult chronic HBV carriers showed a frequency of HBe antigenemia of about 35%, with a significant decreasing trend with age. HBV DNA status generally correlated with the HBe status. An atypical profile of anti-HBe associated with serum HBV DNA is found in some carriers; in most instances, this is related to seroconversion from HBe antigenemia to anti-HBe.

Chronic complications of HBV infection include the development of hepatocellular carcinoma (HCC), the occurrence of which closely parallel that of HBsAg carrier rate. In Malaysia, HCC is the third most common malignant neoplasm and among the 10 leading causes of death. About 80% of four HCC cases are HBV associated. All 3 ethnic groups are afflicted, the highest frequency being among the Chinese. Males show a disproportionate risk with an odds ratio of 3.93 ($p < 0.0001$).

Key words: Hepatitis B virus, hepatocellular carcinoma, epidemiology.

INTRODUCTION

Hepatitis B is recognised as a major public health problem in many parts of the world particularly in developing countries in East Asia, South-East Asia, Africa and the Pacific Basin. In hyperendemic regions which include many countries in Asia and Africa, the Hepatitis B surface antigen (HBsAg) carrier rate ranges from 8% to 20%. In contrast, the carrier rate in most of North America, Australia, Western and Central Europe is low, ranging from 0.1% to 0.5%. In Malaysia, the reported HBsAg carrier rate varies from less than 1% to 10%^{1,2} depending on the ethnic group studied. Malaysia is a multiracial country comprising 3 major ethnic groups – Malays, Chinese and Indians. Based on blood donor statistics of the University of Malaya Teaching Hospital, Kuala Lumpur (UHKL), the highest frequency is among the Chinese (4-7%), followed by the Malays (2-4%) and lastly the Indians (<1%). A male preponderance is evident in our population, with a male to female ratio of 2-3:1. Exposure to the virus is estimated at between 20% to 30%. The highest exposure rate is in the Chinese population (36%), followed by the Malay population (26%) and the lowest

exposure is among the Indians (15%) (UHKL blood donor statistics). There is no apparent difference in the exposure rate between males and females. However, the frequency of the carrier rate compared to the frequency of exposure is higher among males suggesting an increased risk of the carrier state in males. Our data also suggest that the risk of acquiring the carrier state is highest in the Chinese and lowest in the Indians.

Transmission of the infection

A major mode of transmission of the hepatitis B virus (HBV) is perinatal transmission from mother to infant.³⁻⁵ Infection in infancy is followed by the development of the chronic carrier state in over 90% of cases.⁶ In regions of high and intermediate endemicity, maternal to infant transmission is the most frequent form of transmission.^{3,4,7} Serological surveys among Malaysian pregnant women showed a carrier rate of <1% to over 10% based on ethnic origin.^{2,8,9} Between 10-40% of these carrier mothers were hepatitis B e antigen (HBeAg) positive, representing a major risk for transmission of the infection to the infant and providing the impetus

to routinely screen all pregnant women for hepatitis B in Malaysia. The risk of developing the chronic carrier state decreases progressively with age. Adults infected with HBV develop the chronic carrier state in only 5% to 10% of cases. However, the risk of developing chronic HBs antigenaemia is known to be higher among selected groups of adults including homosexual males, parenteral drug users and residents of institutions for the mentally retarded. In a study conducted on patients with sexually transmitted diseases (STD), we found an HBsAg prevalence of 11.3% and 8.1% among males and females respectively.¹⁰ Although this value was higher than that in the control population, the difference was not statistically significant. However, the STD patients demonstrated a higher exposure rate of 64.3% compared to 38.9% in the controls which was statistically significant ($X^2=34.98$ $P<0.0001$). Similarly, we did not find a significant difference in the carrier rate between health care workers and control donor population." We noted, however, that attendants working in the diagnostic laboratory had a significantly high exposure rate of 80% compared to all other health care workers and the donor population. This was clearly the direct consequence of the practice of manual washing of blood sample containers adopted in the laboratory at that point in time. Similar findings were also reported for staff working in the Haemodialysis Unit of a General Hospital.¹²

Chronic HBV infection

Review of the serological status of chronic HBV carriers followed up regularly in our outpatient department showed a frequency of hepatitis B e (HBe) antigenemia of 35% indicating that over a third of these carriers have actively replicating virus and are therefore highly infectious. There was no apparent difference between the three ethnic groups. A significant trend of decreasing HBe antigenemia with age was observed, ranging from about 15% in the over 50 year age group to about 70% in the under 20 year age group. Conversely, seroconversion to anti-HBe increased with age from 30% in the under 20 to 80% in the over 50 year age groups respectively. We noted that a small proportion (1.7%) of carriers were seropositive for both the HBeAg and anti-HBe either as a transient or relatively persistent phenomenon.

The HBV-DNA status of the chronic carriers showed a positive correlation with the HBeAg. The converse was true for anti-HBe positive

carriers. Some HBeAg seropositive carriers did not have detectable HBV-DNA in their sera. In most instances, this was related to imminent seroconversion or was a transient phenomenon. About 10-15% of the carriers were positive for HBV-DNA despite seroconversion to anti-HBe. These individuals often were recent seroconverters or had apparently transient increase in viral replicative activity.

The finding of an atypical profile of anti-HBe associated with evidence of active viral replication has been reported mainly in Oriental and Mediterranean patients – both asymptomatic carriers and patients with evidence of chronic liver disease.¹³⁻¹⁵ This observation led to the discovery of a variant virus with mutations in the precore/core region of the viral genome.^{16,17} A base substitution in the second last codon (nucleotide 1896) of the precore gene resulted in the introduction of a stop codon and the failure to synthesize the protein from which the HBeAg is derived. However, the replication competence of the virus remains intact. Other mutations resulting in interference with HBeAg processing have also been described. The HBeAg negative mutant (HBVe-) appears to be dominant at the time of HBeAg/anti-HBe seroconversion. In some of these cases, the HBVe- continues to replicate in association with the rapid development of progressive liver disease while in others, the HBVe- persists without inflammatory liver disease. Currently, we have no data to show whether or not our seroconverters acquire the HBVe-.

Raised serum transaminases was used routinely as a biochemical marker of hepatic inflammation in our carriers. Overall, transaminases were raised in about half of the carriers who had detectable HBV-DNA in their sera suggesting an association between viral replication and immune response. Conversely, the majority of the HBV-DNA negative carriers had normal enzyme levels. However, there was no discernable relationship between the level of HBV-DNA and enzyme levels.

Data on serological follow-up of asymptomatic HBV carriers over a 9 year period showed that about 16% of the cases who were HBeAg positive at presentation lost the HBeAg and acquired the anti-HBe. Another 2% of cases lost the HBeAg but remained in the e window. Elevation of serum transaminases was associated with seroconversion in about 50% of the cases. However, due to the relatively long duration between follow-up visits, it is not possible to ascertain the true extent of enzyme changes

accompanying HBe seroconversion. We also found reactivation of viral replication (reversion to HBeAg positive status) in 23% of recent HBe seroconverters. Some reactivation events were transient while others lasted from one to several years. During the period of study, only a very small number of carriers lost the HBsAg and acquired the anti-HBs.

Hepatitis B virus related hepatocellular carcinoma

The clinical importance of the HBV carrier state lies in the risk of development of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC).¹⁸⁻²¹ The incidence of HCC closely parallel the prevalence of the HBsAg carrier rate. High rates of HCC are therefore found throughout Asia, Sub-Saharan Africa and Oceania. It is among the leading cancer in South-East Asia and the third most common malignancy among males in Malaysia. It also ranks among the top 10 leading causes of death among Malaysians (Annual Mortality & Morbidity Statistics, Ministry of Health of Malaysia).

About 80% of our cases of HCC are HBV related. The majority of the HCC patients are between the ages of 40 to 70 years. However, about 18% of cases are under 40 years of age and a small proportion are children and adolescents. All 3 ethnic groups are afflicted. The frequency of HCC is highest among the Chinese, followed by the Malays and lastly the Indians. This can be accounted for largely by the difference in the HBV carrier rate in these 3 ethnic groups. Males show a disproportionate risk for the development of the malignancy with an odds ratio of 3.93 ($p < 0.0001$) compared to females. The predisposition of the male sex for the development of HCC is well known and is attributed partly to their higher frequency of the carrier state. Other factors suggested include cigarette smoking, alcohol consumption and the male sex hormone.²²⁻²⁷ We found a higher frequency of smoking and drinking habit among our HCC patients compared to the healthy carrier population. We also found a higher frequency of alcohol intake and cigarette smoking among male HCC patients compared to females. Histological examination of biopsies with adequate parenchymatous tissues for evaluation demonstrated that virtually all our HCC patients had associated liver cirrhosis, an additional aetiological association reported in other studies.²⁸ Continuing inflammatory activity was noted in over 80% of the cases studied. The status of the remaining 20% of HCC cases who were seronegative for the HBsAg is not clear. It

is likely that a proportion of these cases were in fact HBV related but have lost the HBsAg from their sera. It is equally likely that some of these cases were Hepatitis C virus related or alcohol related.

Chronic hepatitis and liver cirrhosis

Chronic liver disease (CLD) and liver cirrhosis (LC) accounts for just over 2% of deaths in Malaysia. Review of the case records of histologically proven cases of chronic hepatitis (CH) and LC in our Medical Centre showed an HBV carrier rate of about 63% and 40% respectively.

Histological evaluation of biopsies from asymptomatic carriers with detectable serum HBeAg, HBV-DNA and raised liver enzymes demonstrated that changes of chronic persistent hepatitis (CPH) was present in 62% of the cases, chronic active hepatitis (CAH) in 29% and mild non-specific changes in the remaining 9%. In other words, about 90% of these cases have evidence of liver involvement. Overall, about 35% of our asymptomatic carriers are HBeAg positive, of whom, about 40% (14% of all carriers) have raised serum transaminases and therefore a 90% chance of having some form of liver disease. It would appear therefore, that an estimated 12-13% of asymptomatic HBV carriers have a risk of inflammatory liver disease.

Extrahepatic infection

Extrahepatic manifestation of HBV infection has traditionally been attributed to circulating immune complexes. More recent data suggests the possibility of infection of extrahepatic tissue by the virus. The biological significance of this remains speculative at this point in time. If non-hepatocytes are able to support viral replication, these cells can serve as a reservoir of infection. Tissues in which viral genomic sequences have been demonstrated include peripheral blood mononuclear cells (PBMCs), pancreas, gall-bladder, bile duct epithelium, liver endothelial cells, lymph nodes, kidneys, adrenals, gonads and thyroid.

In a study involving 200 asymptomatic carriers, we demonstrated the presence of HBV-DNA in the PBMCs of the large majority of cases. Replicating intermediates of the virus and HBV-specific RNA have been demonstrated in mononuclear cells.^{29,30} The detection of episomal molecules of the HBV genome in a cell line derived from the bone marrow of an HBV infected individual further supports the possibility of

replicative activity in lymphoid cells. The clinical significance of the presence of the virus in mononuclear cells remains open to speculation. Suggested roles include pathogenesis of chronic infection and transmission of infection.

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