

Peritoneoscopic Liver Biopsy Findings in Asymptomatic Chronic HBsAg Carriers with Normal Liver Function Tests and No Hepatomegaly

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Asymptomatic chronic HBsAg carriers with normal liver function tests are, in general, regarded as having no liver pathology. Most of the histologic findings in asymptomatic chronic carriers have been reported from areas with low incidence of Hepatitis B virus (HBV) infection, such as North America and Western Europe. It is well known that there are many differences in HBV infection between low and high endemic areas, but there have been few reports on the histologic findings of asymptomatic chronic HBsAg carriers from endemic areas.

The present study was undertaken in Korea which is one of the endemic areas for HBV infection and was designed to assess the prevalence of chronic liver disease by peritoneoscopic liver biopsy among asymptomatic chronic HBsAg carriers and to make a basis for the follow-up of asymptomatic chronic HBsAg carriers according to the results obtained. One hundred and ten asymptomatic chronic HBsAg-positive carriers with normal liver function tests and no hepatomegaly were included in the study. Final diagnosis by peritoneoscopic liver biopsy revealed that of the 110 asymptomatic carriers only 27 (24.5%) had a histologically normal liver, while 51 (46.4%) had chronic liver diseases, and the remaining 32 (29.1%) had nonspecific histologic abnormalities (nonspecific reactive changes in 18 cases, cholestasis in 6 cases, and fatty change in 8 cases). Of the 51 patients with chronic liver diseases, 3 had liver cirrhosis, 4 chronic active hepatitis with cirrhosis, 11 chronic active hepatitis and 33 chronic persistent hepatitis. The frequency of liver cirrhosis and chronic active hepatitis with cirrhosis was significantly high in the over 30 years of age group (12.1%) than in the under 30 years of age group (0%; $p=0.011$ by Fisher's exact test).

In conclusion, 46.4% of the Korean asymptomatic chronic HBsAg carriers with normal liver function tests and no hepatomegaly had chronic liver disease. This finding contrasted with reports from low incidence areas of HBV infection. Our results suggest that in endemic areas, a liver biopsy should be considered to assess the status of liver disease in asymptomatic chronic HBsAg carriers even if liver function tests are normal and hepatomegaly is absent, and the result can be used as a basis for the follow-up of each asymptomatic chronic HBsAg carriers.

Key Words: Hepatitis B, peritoneoscopy, liver histology, HBsAg carriers

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There are now over 250 million Hepatitis B virus (HBV) carriers worldwide, accounting for approximately 5% of the earth's population (Zuckerman, 1983; Anderson and Murray-Lyon, 1985). Prevalences of the Hepatitis B surface antigen (HBsAg) carrier state vary widely. In the United States, as in most but not all, Western nations, HBsAg carriers com-

prise 0.1 to 0.5% of the population (Koff, 1981; Dienstag, 1984). In South-East Asia and the Far East including Korea, and sub-Saharan Africa, the frequency of chronic HBV infection may approach 5 to 20% of the population (Dienstag, 1984).

Chronic HBsAg carriers are considered to be those who have HBsAg in their serum for at least 6 months. However, chronic HBsAg carriers vary markedly in their clinical, biochemical, serologic and histologic features (Brechot *et al.* 1981; Hadziyannis *et al.* 1983; Hoofnagle and Alter, 1984). Indeed, the absence of symptoms does not exclude the presence of significant liver disease. Histologic findings in asymptomatic chronic HBsAg carriers vary enormously according to the proportion of HBsAg carriers with normal liver function tests among the subjects. The prevalence of chronic liver disease was relatively high in Villeneuve *et al.*'s and Feinman *et al.*'s reports in which HBsAg carriers with abnormal liver function tests were included. In contrast, when only HBsAg carriers with normal liver function tests were included, as in Shrago *et al.*'s and Koretz *et al.*'s reports, most of the HBsAg carriers had histologically nonspecific findings rather than chronic liver diseases (Feinman *et al.* 1975; Villeneuve *et al.* 1976; Shrago *et al.* 1977; Koretz *et al.* 1978). Koretz *et al.* summarized the literature on histologic findings of asymptomatic chronic HBsAg carriers with normal liver function tests (237 carriers from 19 publications) and found that the prevalence of significant liver diseases such as cirrhosis or chronic active hepatitis (CAH) was quite low (Koretz *et al.* 1978). Only 5 (2.1%) of 237 carriers had cirrhosis or CAH. Notably, these reports, except one from Taiwan, were from North America and Western Europe where the prevalences of chronic HBsAg carriers among the general population were very low. Although the majority of chronic HBsAg carriers live in endemic areas, there have been few histologic studies of asymptomatic chronic carriers from these areas.

The present study was undertaken to assess the prevalence of chronic liver disease by peritoneoscopic liver biopsy and to make a

basis for the follow-up of asymptomatic chronic HBsAg carriers in Korea according to the results obtained.

MATERIALS AND METHODS

MATERIALS-110 asymptomatic chronic HBsAg carriers who were admitted to Yonsei University Severance Hospital, Seoul, Korea from June 1984 through March 1994 were selected for this study. The most common reason for HBsAg testing was annual routine physical examination at work (82 cases; 74.5%). Others were identified on screening before hepatitis B vaccination (9 cases; 8.2%), because of HBsAg-positive family members (7 cases; 6.4%), testing before blood donation (5 cases; 4.5%), and for miscellaneous reasons (7 cases; 6.4%). Strict inclusion criteria were applied. All subjects were required to have HBsAg in their sera for longer than 6 months, no past history of acute viral hepatitis within 6 months, no past history of other liver diseases, normal liver function tests on two occasions at least 6 months apart, and no hepatomegaly on physical examination and liver scintigraphy or abdominal ultrasonography. Ages of HBsAg carriers ranged from 17 to 52 years, with a mean of 31.0 years. Peak incidence was found to be the 3rd and 4th decades (77 cases; 70.0%), and the male (80 cases) to female (30 cases) ratio was 2.7 to 1.

METHODS-Hepatitis B virus markers (HBsAg, anti-HBs, anti-HBc, HBeAg, and anti-HBe) were determined by radioimmunoassay kits. HBsAg was assayed by AUSRIA kit; anti-HBs, AUSAB kit; anti-HBc, CORAB kit; HBeAg and anti-HBe, Abbott HBe (all Abbott Pharmaceuticals, North Chicago IL, USA). Peritoneoscopy was performed by the reference technique and liver biopsy under direct vision was done with a Vim-Silverman needle in all 110 HBsAg carriers. The liver biopsy specimens were fixed with a 10% buffered formalin, embedded in paraffin, and examined for histologic findings under light microscopy after the Hematoxylin-Eosin stain and/or the reticulin stain. Peritoneoscopic and histologic

findings were compared, and a final diagnosis was made on the basis of both the peritoneoscopic and the histologic findings. Finally, the prevalence of chronic liver disease was compared with regard to age, sex and the HBeAg/anti-HBe status.

RESULTS

HBsAg and anti-HBc were positive and anti-HBs negative in all 110 subjects. HBeAg and anti-HBe were determined in 90 out of the 110 carriers. HBeAg only was positive in 39 cases (43.3%), anti-HBe only was positive in 47 cases (52.2%) and both were negative in 4 cases (4.4%).

The peritoneoscopic and histologic findings and the final diagnosis of the 110 asymptomatic chronic HBsAg carriers are shown in Table 1. Forty-nine (44.5%) of the 110 chronic HBsAg carriers had chronic liver disease by peritoneoscopic findings, whereas 50 (45.5%) of the 110 carriers had chronic liver disease histologically.

There were minor discrepancies between the peritoneoscopic and the histologic findings.

Final diagnosis was made based on both findings and was consistent with the histologic findings in all but 2 cases. Two cases with peritoneoscopic evidence of CAH with cirrhosis had histologic findings of chronic persistent hepatitis (CPH) and nonspecific reactive hepatitis, respectively; however, the final diagnosis in each was felt to be CAH with cirrhosis on the basis of the peritoneoscopic findings. There were 51 cases (46.4%) of chronic liver disease and 27 cases (24.5%) with histologically normal liver.

The finding of chronic liver disease was correlated with regard to age, sex, and HBeAg/anti-HBe status (Table 2). There were no significant differences in the frequency of chronic liver disease (liver cirrhosis, CAH with cirrhosis, CAH and CPH) between the group over 30 years of age (46.6%) and the group under 30 years of age (46.4%). However, the frequency of liver cirrhosis and CAH with cirrhosis was significantly higher in the over 30 years of age group (12.1%) than in the under 30 years of age group (0%; $p=0.011$ by Fisher's exact test). No significant difference was found in the frequency of chronic liver disease between male (50.0%) and female (36.7%). Furthermore, no statistically significant differ-

Table 1. Peritoneoscopic, histologic findings and final diagnosis in asymptomatic chronic carriers

	Peritoneoscopic findings No. of cases(%)	Histologic findings No. of cases(%)	Final diagnosis No. of cases(%)
Chronic liver disease	49(44.5)	50(45.5)	51(46.4)
Liver cirrhosis	3(2.7)	3(2.7)	3(2.7)
CAH with cirrhosis	4(3.6)	2(1.8)	4(3.6)
CAH	21(19.1)	11(10.0)	11(10.0)
CPH	21(19.1)	34(30.9) ^a	33(30.0)
Nonspecific findings	5(4.5)	33(30.0)	32(29.1)
Fatty liver		8(7.3)	8(7.3)
NRH		19(17.3) ^a	18(16.4)
Cholestasis		6(5.5)	6(5.5)
Normal liver	56(60.9)	27(24.5)	27(24.5)
Total	110(100.0)	110(100.0)	110(100.0)

a.b: Each case was finally diagnosed as having CAH with cirrhosis based on the peritoneoscopic findings, even though histologic finding was CPH and NRH, respectively.

CAH: Chronic active hepatitis

CPH: Chronic persistent hepatitis

NRH: Nonspecific reactive hepatitis

Table 2. The prevalence of chronic liver disease with regard to age, sex, and HBeAg/anti-HBe status

	Chronic liver disease					Nonspecific findings(%)	Normal liver(%)	Total
	Liver cirrhosis	CAH with cirrhosis	CAH	CPH	Total			
Age(yrs)								
<30	—	—	7	17	24(46.2)	15(28.8)	13(25.0)	52
>30	3*	4*	4	16	27(46.6)	17(29.3)	14(24.1)	58
Male	1	2	9	28	40(50.0)	22(27.5)	18(22.5)	80
Female	2	2	2	5	11(36.7)	10(33.3)	9(30.0)	30
HBe(+)	1	1	4	12	18(46.2)	10(25.6)	11(28.2)	39
Anti-HBe(+)	1	1	4	14	20(42.6)	15(31.9)	12(25.5)	47
Both(—)	—	—	1	1	2(50.0)	2(50.0)	—	4

CAH: Chronic active hepatitis

CPH: Chronic persistent hepatitis

*: The frequency of liver cirrhosis and CAH with cirrhosis was significantly higher in the group of patients over 30 years of age(12.1%) than in the group of patients under 30 years of age(0%; $p=0.011$ by Fisher's exact test).

ence was seen in the frequency of chronic liver disease between the HBeAg-positive group (46.2%) and the anti-HBe-positive group (42.6%).

DISCUSSION

The term 'chronic HBsAg carrier' is usually used to designate persons who have had HBsAg in their serum for at least 6 months. The term 'asymptomatic carriers' is often applied because most carriers are asymptomatic at the time of recognition. However, chronic HBsAg carriers vary enormously in their clinical, biochemical, serologic and histologic features (Brechot *et al.* 1981; Hadziyannis *et al.* 1983; Hoofnagle and Alter, 1984). Hoofnagle *et al.* suggested that chronic HBsAg carriers could be divided into two groups; (i) those with chronic liver disease and (ii) those without (Hoofnagle *et al.* 1987). The first group is usually referred to as having a 'chronic HBsAg carrier state'. Distinguishing between chronic hepatitis B and the asymptomatic healthy chronic HbsAg carrier state is clinically important because these different forms of chronic HBV infection may have different

outcomes.

HBsAg carriers without subjective symptoms or signs of liver disease may or may not have chronic liver disease. Sakuma *et al.* proposed that biochemical liver function tests had limitations in the assessment of liver disease, particularly in the diagnosis of stable cirrhosis or chronic active hepatitis in which serum aminotransferase levels tend to be normal (Sakuma *et al.* 1982). Differentiation of the two categories of patients with chronic HBV infection requires histologic study. There have been varying results among reports concerning histologic findings in chronic HBsAg carriers. One reason for the differences is likely to be the proportion of HBsAg carriers with abnormal liver function tests among the subjects studied. Some authors included HBsAg carriers with abnormal liver function tests and reported relatively high frequencies (84.2%, 72.5%, 44.2% respectively) of chronic liver disease (Woolf *et al.* 1974; Feinman *et al.* 1975; Ville-neuve *et al.* 1976). In contrast, others reported very low frequencies (0%, 4.2% respectively) of chronic liver disease in asymptomatic HBsAg carriers with abnormal liver function tests (Reiniche *et al.* 1972; Vittal *et al.* 1974). On the other hand, Shrago *et al.*, Koretz *et al.*, and Liaw and Sung included only the HBsAg car-

riers with normal liver function tests and reported that most of the HBsAg carriers had nonspecific histologic findings rather than those of chronic liver disease (Shrago *et al.* 1977; Koretz *et al.* 1978; Liaw and Sung, 1979). Koretz *et al.* summarized literature (19 publications) on the histologic findings in asymptomatic HBsAg carriers with normal aminotransferase levels and concluded that the frequency of significant liver disease such as cirrhosis or chronic active hepatitis was quite low (2.1%) (Koretz *et al.* 1978).

The present study showed a high frequency of chronic liver disease in asymptomatic chronic HBsAg carriers; 18 (16.3%) of the 110 chronic HBsAg carriers had cirrhosis and/or CAH and 33 (30.0%) had CPH. Overall, 51 (46.4%) of the 110 HBsAg carriers had chronic liver disease. This finding is quite different from the results of the previous reports on this issue. It is important to point out that all but one study reviewed by Koretz *et al.* were from North America and Western Europe where the HBsAg carrier rate among the general population is quite low, and infection usually occurs in adulthood and is related to contact with either infected blood or blood products (Koretz *et al.* 1978). The present study was undertaken in Korea, a region endemic for HBV and where HBV infection usually occurs at birth or in infancy. The prevalence of chronic liver disease in asymptomatic chronic HBsAg carriers with normal liver function tests may well be different between the areas of high and low prevalences of HBV infection. The final diagnosis in this study was based on both peritoneoscopic and histologic findings. Two cases showed a disparity between the peritoneoscopic and the histologic findings; a diagnosis of CAH with cirrhosis by peritoneoscopy contrasted with histologic findings of chronic persistent hepatitis and nonspecific reactive hepatitis in the two patients, respectively. However, the final diagnosis in each case was felt to be CAH with cirrhosis on the basis of the definite peritoneoscopic findings. There is some possibility of sampling error in both peritoneoscopic and blind liver biopsies. However, a final diagnosis can be made based on well-defined peritoneo-

scopic findings in cases in which there is a disparity between the peritoneoscopic and histologic findings. Theoretically it would have been ideal to have compared the frequency of chronic liver disease between the asymptomatic HBsAg-negative and positive subjects with normal liver function tests but peritoneoscopy and liver biopsy would not have been justifiable in the HBsAg-negative controls.

There have been few reports on the frequency of chronic liver disease with regard to age and sex in asymptomatic chronic HBsAg carriers. De Franchis *et al.* found that specific histologic lesions were evenly distributed among the various age groups and that there were no sex differences (De Franchis *et al.* 1980). In this study, the frequency of chronic liver disease in the group of patients over 30 years of age (46.6%) was similar to that of the group of patients under 30 years of age (46.2%) and no statistical difference was found. However, the frequency of liver cirrhosis and CAH with cirrhosis was significantly higher in the over 30 years of age group (12.1%) than in the under 30 years of age group (0%; $p=0.011$ by Fisher's exact test). There was no difference in the frequency of chronic liver disease between the asymptomatic male and female chronic HBsAg carriers. These results were consistent with those of De Franchis *et al.* (1980).

Limited cross-sectional studies have suggested that the detection of HBeAg in the chronic HBsAg carriers correlates poorly with liver histology. Koretz *et al.* reported that only 2 HBeAg-positive carriers consented to liver biopsy and that both had chronic persistent hepatitis (Koretz *et al.* 1978). In this study, 46.2% of HBeAg positive carriers and 42.6% of anti-HBe positive carriers had histologically proven chronic liver diseases. There was thus no difference in the frequency of chronic liver disease between these groups.

Many authors have concluded that the incidence of significant liver disease such as cirrhosis and/or CAH in chronic HBsAg carriers with normal liver function tests is too low to justify the risk and expense of liver biopsy and that liver biopsy should be restricted to chronic HBsAg carriers with abnormal liver

function tests (Sun *et al.* 1976; Koretz *et al.* 1978; Liaw and Sung, 1979; Gonzalez-Molina *et al.* 1980; Dragosics *et al.* 1987). However, 46.4% of asymptomatic chronic HBsAg carriers with normal liver function tests in this study had chronic liver disease. These results suggest that only the liver biopsy can differentiate chronic hepatitis B from the asymptomatic chronic HBsAg carrier state, and the result of such biopsy can be used as a basis for the follow-up of asymptomatic chronic HBsAg carriers, such as the screening test of hepatocellular carcinoma.

In summary, of the 110 Korean asymptomatic chronic HBsAg carriers with normal liver function tests and no hepatomegaly, 51 (46.4%) had chronic liver disease and 18 (16.3%) had significant liver disease such as liver cirrhosis (3), CAH with cirrhosis (4) and CAH (11). There thus appears to be a marked difference in the prevalence of significant liver disease between low and high incidence areas for HBV infection. This study suggests that in endemic areas for HBV infection, liver biopsy should be considered to assess the exact status of liver disease in asymptomatic chronic HBsAg carriers, even if liver function tests are normal and hepatomegaly is absent, and the result can be used as a basis for the follow-up of each asymptomatic chronic HBsAg carrier.

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