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Clinical and pathological study of asymptomatic HBsAg carriers in Chile

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SUMMARY A clinical, biochemical, and pathological study was performed in 38 chronic HBsAg carriers. The study group is a part of 393 carriers found among 117 705 voluntary blood donors at the National Blood Bank, Hospital del Salvador, Santiago, Chile. None of the 38 carriers had a past history of illicit drug abuse, hepatitis, or work involving a high risk of hepatitis B virus infection. Ten individuals had a normal liver biopsy, 17 reactive non-specific hepatitis, one fatty changes, four chronic persistent hepatitis, one aggressive hepatitis, two post-necrotic cirrhosis, and three alcoholic cirrhosis. There was not a close correlation between liver function test and liver histology. The most significant laboratory finding was the positivity of alpha fetoprotein in two cases. During the follow-up the two alpha fetoprotein patients presented a hepatocarcinoma 12 and 14 months after admission to the study.

Since the discovery of the Australia antigen (Blumberg *et al.*, 1965) and its association with the hepatitis B virus (Prince, 1968; Blumberg *et al.*, 1970), a group of asymptomatic carriers of the antigen has been identified together with acute and chronic hepatic disease (Gocke *et al.*, 1970; Cherubin and Prince, 1971; Berris *et al.*, 1973; Szmunness *et al.*, 1973).

The number of these asymptomatic carriers varies from one country to another (Prince, 1970; Salzano *et al.*, 1970) and depends on many factors such as the social behaviour of the population (Mazzur and Jones, 1977), drug addiction (Cherubin *et al.*, 1970), use of commercial blood (Alter *et al.*, 1975), and family clustering (Blumberg *et al.*, 1969; Velasco *et al.*, 1973; Szmuness *et al.*, 1975).

The prognosis of these individuals has not been defined exactly, although the literature reveals that there is some degree of abnormality on liver biopsy in the majority of asymptomatic carriers (Prince *et al.*, 1969; Reinicke *et al.*, 1972; Simon and Patel 1974; Shrago *et al.*, 1977).

In an attempt to determine the prognosis of the asymptomatic HBsAg carriers in Chile we undertook a clinical and pathological study of those individuals whose blood had been positive for HBsAg for at least four months.

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Methods

Blood donation is voluntary in Chile. Since 1972, all blood donors in the National Blood Bank, Hospital del Salvador, Santiago, are screened routinely for the presence of HBsAg, by the counterimmunoelectrophoresis method using standardised antisera to HBsAg.

Up to December 1976, 393 HBsAg positive individuals were found among 117 705 voluntary blood donors. They were urged through correspondence to undergo a clinical examination and be retested for HBsAg in the blood.

One-hundred-and-fifty donors positive for at least four months were examined and laboratory study performed. Thirty-eight of these were eligible for liver biopsy and were followed up regularly at intervals of six months. The minimum follow-up period was six months, 14 were followed up for more than 12 months, and 20 for more than 24 months.

These carriers were submitted to a complete clinical examination; liver function tests (serum bilirubin, alkaline phosphatase, SGPT, prothrombin time, bromsulphthalein retention test); serum levels of immunoglobulins (Ig G, Ig M, Ig A) and C_3 by the Mancini test; alpha fetoprotein by immunodiffusion and haemagglutination.

Liver biopsies were performed in the 38 cases with a Menghini needle and studied in a paraffin-

embedded tissue, stained with haematoxylin-eosin and by a reticulum method. The following features were analysed: lobular architecture; portal tract, central vein and intralobular infiltrates; fibrosis; lobular limiting plates, cell pleiomorphism, ground-glass cytoplasm, hyperplasia of the Kupffer's cells, and fatty changes. The pathologist made his report without knowledge of the clinical or laboratory findings.

Results

The group consisted of eight women and 30 men with a mean age of 28 years (range, 18 to 48 years). None of the carriers had a history of illicit drug abuse, recent contact with hepatitis, or occupation associated with an increased risk of hepatitis B infection. Three donors were alcoholics.

The first physical examination was normal in all but one alcoholic carrier who had moderate hepatomegaly.

Results of liver function tests were as follows: normal serum bilirubin in all except in the one alcoholic individual. Alkaline phophatase was slightly raised in 16 and markedly raised in one. SGPT was slightly raised in only two of 38 cases. Prothrombin time was normal in all cases. Bromsulphthalein retention was normal in 24, borderline in eight, and clearly abnormal in six.

Ig G levels were slightly raised in 24, Ig M in 12, and Ig A in 30 cases. C_3 was normal in 36 cases, being slightly low in the other two.

Alpha fetoprotein was present in two.

LIVER HISTOLOGY

The results of the biopsy were correlated with the liver function tests and the findings are set out in the Table.

Table *Correlation of histological lesions in HBsAg carriers and liver function tests*

Histological findings	*No.*	*Liver function tests*		
		Group 1 Normal	*Group 2 Abnormal*	
			Slightly	*Clearly*
Normal	10	6	4	
Reactive non-specific hepatitis	17	11	5	1
Fatty changes	1	1		
Chronic persistent hepatitis	4	1	1	2
Aggressive hepatitis	1			1
Post-necrotic cirrhosis	2		2	
Alcoholic cirrhosis	3			3
Totals	38	19	12	7

CLINICAL AND HISTOLOGICAL FOLLOW-UP

During the follow-up the HBsAg remained present in all cases. All carriers but three continued to be asymptomatic and with no significant changes in liver function rests. Eight liver biopsies performed in this group did not differ from the first study.

The other three patients developed in the following way: one patient with postnecrotic cirrhosis deteriorated. The two other cases deserve special mention. Both were male, 24 and 28 years old. When first seen the first patient had a normal liver with normal liver function tests and the second showed chronic persistent hepatitis with abnormal liver function tests (alkaline phosphatase 18 KA units). Both patients were alpha fetoprotein positive. In the second patient hepatic scanning showed a uniform distribution of the isotope within the liver and an increased activity in the spleen.

The first patient presented 12 months later with abdominal pain, rapid weight loss, and a very large nodular and rock-hard liver. Laparoscopy and liver biopsy confirmed a primary carcinoma of the liver without cirrhosis. Liver function tests showed a slight increase in serum bilirubin, alkaline phosphatase of 18 KA, and bromsulphthalein retention 20% at 30 minutes.

The second patient developed mild diarrhoea, anorexia, weight loss, abdominal pain, a marked enlarged nodular liver, and splenomegaly after 18 months. The liver specimen showed hepatocellular carcinoma. Liver function tests were as follows: serum bilirubin of 1·8 mg per 100 ml., alkaline phosphatase of 24 KA, prothombin time of 45%, and bromsulphthalein with retention at 30 minutes; alpha fetoprotein remained positive in the two cases.

Discussion

The ultimate prognosis of the carrier state of hepatitis B virus infection remains uncertain. In our study only 10 out of 38 asymptomatic carriers had normal liver histology. In three heavy alcoholics, alcoholic cirrhosis was found. In 22 cases the lesions found were considered to be minor and in three severe.

Is the coexistence of hepatocarcinoma with the hepatitis B virus fortuitous or pathogenetically related?

In Chile, where necropsy is mandatory in patients who die in a hospital, the incidence of hepatocarcinoma is low. However 70% of the hepatocarcinomas are HBsAg positive (Velasco *et al.*, 1971). The incidence of the HBsAg in the Chilean general population is 0·3% and in carrier families 14%. In a familial study of these chronic carriers

we found that four out of 23 families had one or more siblings, with a confirmed hepatocarcinoma (Velasco *et al.*, 1973). Recently we have seen a patient with chronic aggressive hepatitis who was HBsAg positive, whose sister had a postnecrotic cirrhosis and whose mother died of primary carcinoma of the liver. In the literature, cases of familial hepatocarcinoma have been reported (Denison *et al.*, 1971). To our knowledge this is the first report in which a hepatocarcinoma appeared in the follow-up study of an asymptomatic HBsAg carrier. All these observations support the idea of a possible oncogenic role of the hepatitis B virus.

Investigation of alpha fetoprotein seems most important in asymptomatic chronic carriers. In our two patients in whom a hepatocarcinoma appeared the test was positive many months before the emergence of the tumour.

It has been postulated that the carrier state depends on a relative immunological defect against the hepatitis B virus (Dudley *et al.*, 1972). A lack of response to stimulation of lymphocytes to HBsAg has been shown in chronic carriers (Millman *et al.*, 1971; Sutnick *et al.*, 1973).

It is possible that this group of asymptomatic carriers is a heterogeneous one. Some of these individuals have a mild chronic process with an ultimately good prognosis, while others progress to severe or irreversible damage.

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