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Outcome of Inactive Carriers of HBV in 10 Years Follow-Up in Iran.

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ABSTRACT

In patients of hepatitis B the natural progress of hepatitis B is different from inactive carriers of hepatitis to cirrhosis and hepatocellular carcinoma. The largest group of chronic hepatitis is inactive carriers of hepatitis B. The prognosis of inactive carriers of hepatitis B is usually good, but rarely in these patients, the disease becomes active again, progresses and leads to serious liver damage; therefor, planning for routine monitoring of patients is very important. This study was conducted in Hepatitis Clinic associated with Blood Transfusion Organization and labbafi nezhad hospital in Tehran in 2003-2013. The patients were selected randomly.Inactive carriers of hepatitis B were followed for 5-10 years. 420 patients had been studied for 5 years, and 73 of them had been studied for 10 years. In a 5-year study,83.3% of patients remained Inactive carriers. From 73 patients who were studied for 10 years, 94.5% remained inactive carriers. Chronic hepatitis had been reported as 4.3% in the 5-year study and 1.4% in the 10-year study. A low percentage of patients showed adverse outcomes such as chronic hepatitis and no cases of cirrhosis or hepatocellular carcinoma were reported But the disease rarely reactivates spontaneously in inactive carriers of hepatitis B so Follow-up of healthy carriers of hepatitis B is very important.

Keywords: HepatitisB,chronic;inactive carrier;outcome.

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INTRODUCTION

Hepatitis B belongs to picornaviridae family of viruses containing DNA.Approximately 5% of people have chronic hepatitis B and more than 600000 people die each year due to this disease [1]. genotype D is the most common genotype in Iran and according to WHO classification, Iran has a low to intermediate HBV prevalence , and it is estimated that a bout 1.5 million people are living with HBV infection [2]. due to the vaccination program prevalence of HBV, particularly among the younger generation is reported to have declined in recent years in Iran [3].

The virus multiplies in the blood,therefore any contact of parental or mucosal with infected blood can cause disease.HBV is also found in the other body fluids to a variable degree including semen, saliva, cervical secretions and tears and can survive up to 7 days on enviromental surface. HBV is not found in urine, sweat or stools. Prinatal infection is the predominant mode of transmission in high –prevalence areas, whereas horizontal transmission, particularly in early childhood,accounts for most cases of chronic HBV infection in intermediate prevalence areas.[1] The disease spectrum is different from inactive carrier to cirrhosis and hepatocellular carcinoma.

The ‘‘inactive HBV carrier state’’ may follow seroconversion from HBeAg to anti-HBe antibody. It is characterized by very low or undetectable serum HBV DNA levels and normal serum aminotransferases. A minimum follow-up of 1 year with alanine aminotransferase (ALT) levels at least every 3–4 months and serum HBV DNA levels is required before classifying a patient as inactive HBV carrier.

ALT levels should remain persistently within the normal range according to traditional cut-off values (approximately 40 IU/ml) [14] and HBV DNA should be below 2000 IU/ml.[4] Two different scenarios have been proven to exit : inactive hepatitis B Virus carriers and patients with chronic hepatits B with transient virological and biochemical remission[5,6].

‘‘HBeAg-negative CHB’’ may follow seroconversion from HBeAg to anti-HBe antibodies during the immune reactive phase or may develop after years or decades of the inactive carrier state [4]. HBeAg-negative CHB is associated with low rates of prolonged spontaneous disease remission[7,8].

Most patients become inactive carriers after spontaneous HBeAg seroconversion with good prognosis but progression to HBeAg negative chronic hepatitis due to HBV variant not expressing HBeAg occures at a rate of 1–3 per 100 person years following HbeAg seroconversion [9]. HBsAg loss and seroconversion to anti–HBs antibody may occur spontaneously in 1–3% of cases per year, usually after several years with persistently undetectable HBV DNA [10].

Objectives

The prognosis of inactive carriers of hepatitis B is usually good. Long-term follow-up of these patients showed that in most patients, the disease is biochemically stable and the risk of cirrhosis and hepatocellular carcinoma is very low.

The disease rarely reactivates spontaneously in inactive carriers of hepatitis B and repeated periods of disease activation or continuous activation of the disease can lead to liver damage and even liver failure.

Therefore, assessing the consequences of inactive carriers of hepatitis B is important for better planning for follow-ups and treatments of patients and preventing irreversible effects.

PATIENTS AND METHODS

This observational cohort study was conducted in hepatitis B clinic associated with Tehran Blood Transfusion Organization and labbafi nezhad hospital in 2003-2013. A questionnaire including demographic characteristics, the way to knowthe disease, risk factors, family history of disease and related laboratory indices were prepared.Patients were selected randomly.

Those patients were enrolled visited the clinic at least 3–4 times in a year and their ALT was in a

normal range (40IU/mL) and the amount of virus reported as non-measurable or below 2000 IU/mL. Patients had negative results for HBeAg and seroconversion to HBeAb had been occurred. 73 patients for 10 years and 420 patients for 5 years were followed-up. Patients were visited at least twice a year and the viral load was measured periodically. In each visit, patients were evaluated for general, clinical and LFT (liver function test).In the event of a rise in liver enzymes, viral count and ultrasonography were performed for patients and based on the results a treatment plan had been planned for these patients.

Statistical Analysis

After collecting and recording the information from questionnaires, data was analyzed using software with descriptive studies such as SPSS19. Consequences of inactive carriers of hepatitis B in 5-10 years were identified and its association to age, gender and education was analyzed.

For describing conditions, frequency percentage, average and percentages were used.Chi–square tests, t–tests and analysis of variance (its non–parametric analysis if necessary) were used as shown in tables and graphs.

RESULTS

This study included 420 patients with amean age of 47 years. Most participants in this study were males, married, having a diploma, Fars, from Tehran, self-employed and older than 50 years.420 patients for 5 years and 73 patients for 10 years were studies. 62.1% were male and 38.6% of patients were over 50 years.

89.3% were married and most of them (41%) had a diploma. Regarding race, most of them (67.6%) were Fars;it is justifiable as the study was conducted in Tehran.

Patients were reviewed regarding the way they knew about their disease;most patients (44%) knew their disease through blood transfusion organization after donating blood. 31% of patients became aware of their disease through routine testing. 2.9% of patients reported a history of jaundice.Risk factors were examined. The greatest risk factor (15.5%) was related to the history of dental surgery.After 5 years of follow–up, 83.3% of patients remained inactive carriers of hepatitis B, this value in a 10-year study on 73 patients was 94.5%.The disease reactivated in 4.3% of patients in 5-year follow–up and in 1.4% of patients in 10–year follow–up studies.

In 5–year follow–up study, HBsAg disappeared in 5.7% of patients and in 6.7% seroconversion occurred.No cases of hepatocellular carcinoma or cirrhosis were reported.

DISCUSSION

This was an observational cohort study performed on a cohort of 420 patients with HBV infection who were followed for a period of 5–10 consecutive years.

Among all cases 33.8% had positive family history of hepatitis B indicating the importance of familial transmission of HBV as vertical transmission and horizontal in childhood.

At the end of 5–year follow up HBsAg disappeared in 5.7% of patients and in 6.7% seroconversion occurred and after 5-year follow up. 83.3% of patients remained inactive carrier of HBV, this value in a 10-year study of 73 patients was 94.5% that approximately was similar to previous information from study in 1989–2000 [11].

According to a study from Taiwan during a median follow up period of 8.6 years, 66.8% showed sustained remission [12]. In another study from Greece in 23.8% of patients reactivation of the disease with elevated ALT and positive HBV DNA was recorded during the follow up [13]. In our study the disease reactivated in 4.3% of patients in 5–year follow up and in 1.4% of patients in 10–year follow up.

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The findings of another study do not supported the presence of significant hepatic fibrosis or necroinflammation among Egyptian inactive HBsAg carriers[14], also in our study no case of hepatocellular carcinoma or cirrhosis were reported.

Table1: Distribution of Demographic Variables in the Study

Variable	Level	Number	Percentage
Gender	Male	261	62.1%
	Female	159	37.9%
Age	Under 30	50	11.9%
	31 to 40	82	19.5%
	41 to 50	126	30.0%
	above 50	162	38.6%
Marital Status	Single	45	10.7%
	Married	375	89.3%
Education	Under diploma	163	38.8%
	Diploma	172	41.0%
	AA	13	3.1%
	Bachelor degree or higher	72	17.1%
Race	Fars	284	67.6%
	Turk	81	19.3%
	Lor	35	8.3%
	Others	20	4.8%
Province	Tehran	226	53.8%
	Other than Tehran	194	46.2%
Occupation	Self Employed	143	34.0%
	Employed	66	15.7%
	Retired	46	11.0%
	Housewife	123	29.3%
	Worker	24	5.7%
	Others	18	4.3%

Table 2: depicts information on how patients became aware of their disease, risk factors and family history of disease.

Variables	Level	Number	Percentage
How to Diagnosed	Blood Donation	185	44.0%
	Symptoms	3	0.7%
	Positive Case in Family	100	23.8%
	Check up	130	31.0%
	Unknown	2	0.5%
HistoryofIcterus	No	408	97.1%
	Yes	12	2.9%
Historyof Tattooing	No	403	96.0%
	Yes	17	4.0%
Historyof Cupping	No	367	87.4%
	Yes	53	12.6%
Historyof IDUs	No	419	99.8%
	Yes	1	0.2%
Historyof Extramarital Sex	No	420	100.0%
	Yes	0	0.0%
Historyof Transfusion	No	406	96.7%
	Yes	14	3.3%
Historyof Mouth Surgery	No	355	84.5%
	Yes	65	15.5%
Historyof War Injury	No	415	98.8%
	Yes	5	1.2%
Historyof Intra Familial	No	278	66.2%
	Yes	142	33.8%

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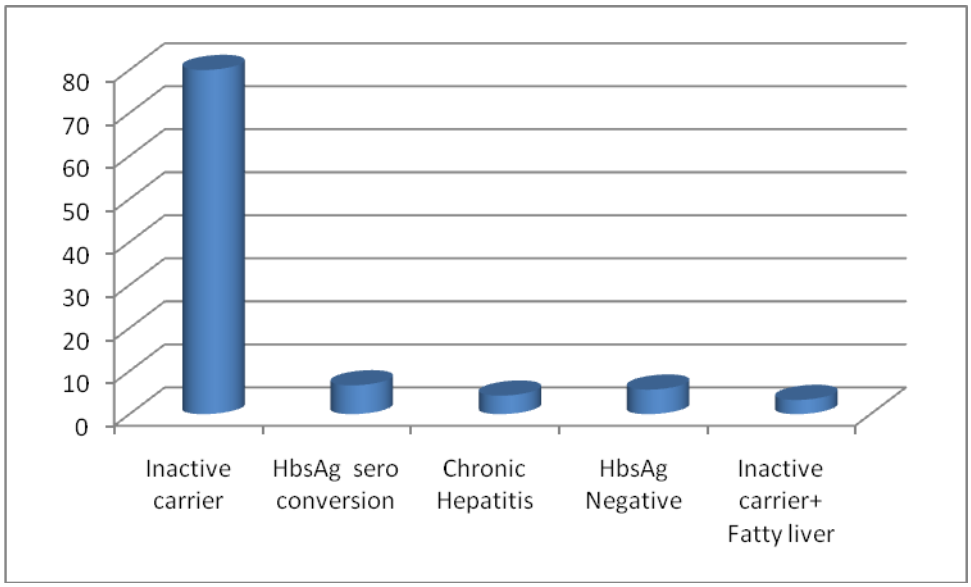
Table 3: The Outcome of Patients after 5 and 10 Years Follow-up

Level	Results of 5-year follow-up		Results of 10-year follow-up	
	Frequency	Percentage	Frequency	Percentage
Inactive Carrier	336	80.0	63	86.3
HBsAg Seroconversion	28	6.7	2	2.7
Cirrhosis	0	0	0	0
Chronic Hepatitis	18	4.3	1	1.4
HBsAg Negative	24	5.7	1	1.4
Inactive Carrier+Fatty liver	14	3.3	6	8.2
Total	420	100	73	100



Variable Frequency Disribution Graph After 5 years of follow-up

According to the obtained results, outcome of carriers of hepatitis B in Iran is desirable (probably due to genotype D).In one study from our country (Iran) elevation of ALT levels,even in the absence of HBV replication increased the risk for the development of CHB up to 8-fold in prospective follow–ups. HBsAg seroclearance, cirrhosis and hepatocellular carcinoma were detected in 10.8% , 1% and 0.25% patients respectively.Fluctuations in serum ALT levels may change the prognosis of HBV inactive carrier state. [18] The probability of spontaneous reactivation of disease,progression of liver damage and cirrhosis and hepatocellular carcinoma is very low, but it is not unlikely. Prognosis is improved by loss of HBsAg but HBsAg clearance does not completely prevent occurrence of decompensation of HCC in patients who have already developed cirrhosis [16,17].

It has been reported that advanced age at study entry [19,20]male gender, HBV DNA $\geq$ 1000IU/ml at study entry [21] HBsAg level $\geq$ 1000 IU/ml at study entry [22] and genotype B[21] or C[23] of the virus may increase the risk for reactivation of the infection into chronic HBeAg negative hepatitis. According to another study in Taiwan risk of developing hepatocellular carcinoma for inactive HBV carriers was higher for those who had detectable baseline serum HBV DNA levels than those with undetectable baseline serum HBV DNA levels [24].

Overall, routine monitoring of inactive carriers of hepatitis B is very important, and based on the outcomes of study, follow–up of patients twice a year seems to be enough. Family screening with HBsAg and HBsAb is necessary, if are negative vaccinate them and success of vaccination should be confirmed with HBsAb testing. Protected sexual intercourse until partner has developed protective antibodies is very important [15].

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