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Screening for Hepatocellular Carcinoma in Chronic Carriers of Hepatitis B and C in Markazi Province, Iran

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Background and Aims: **Chronic HBV and HCV infections are known as important underlying causes of hepatocellular carcinoma (HCC). Their prevalence in Iran are estimated to be 1.7-5% and 0.5-1%, respectively. We investigated the prevalence of HCC in chronic carriers of HBV and HCV via alpha-feto protein (AFP) measurement and ultrasonography as well as pathological assessments.**

Methods: **In this cross-sectional study, HBV and HCV positive cases were determined from documents in blood banks since 1985. From 1064 aviable cases, 514 were randomly selected and followed up for two consecutive years. For all patients, AFP testing and sonography were done after reconfirmation of chronicity. Cases with nodules or mass in sonography and AFP levels above 20 ng/ml were considered suspicious for HCC and after rechecking were referred for liver biopsy. Finally, HCC was confirmed pathologically.**

Results: **The mean subjects' age was 35.19±13.16 years and hepatitis duration was 6.12±5.66 years. Twenty-nine (5.7%) had elevated AFP and 18 (3.5%) had nodules in sonogram. In 16 (3.13%) cases, HCC was detected pathologically. Risk of HCC was correlated with age >40 years, cirrhosis and hepatitis duration (P<0.001). There was no correlation between the risk of HCC and the type of hepatitis, HBeAg positivity, sex and ALT levels.**

Conclusions: **Early screening for HCC using AFP and sonography can be useful for HCC detection in HCV and HBV chronic carriers.**

Keywords: **Hepatocellular Carcinoma, Hepatitis B, Hepatitis C, Alpha-Feto Protein**

Introduction

Hepatocellular carcinoma (HCC), the most common primary liver malignancy, ranks as the fourth most common cancer in the world [1-3]. The long term prognosis for HCC remains poor with a 5 year survival rate of <5% [1, 2]. Its world-wide incidence is estimated to be 500,000-1 million new cases per year, although it varies considerably among geographic locations [2-4]. The age-specific incidence is estimated to be around 3 and 80 per 100,000 people in North America and China, respectively [5], the highest rate being found in Sub-Sahara in Africa, as well as East and Southeast Asia [5, 6]. The most likely explanation for the high rates in the latter areas is the high prevalence of chronic hepatitis B, a strong risk factor for HCC [6].

Recent studies have shown a marked and steadily increasing incidence HCC worldwide [7].

Several other contributing risk factors including chronic hepatitis C, alcoholic cirrhosis, cryptogenic cirrhosis, obesity and diabetes have also been

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identified [8-14]. The prevalence of chronic carriers of HBV and HCV in Iran, according to estimates from blood banks data, are 0.5-3% and 0.05-0.1.7%, respectively [15, 16]. It seems, however; to be an underestimation, as many people who are aware of their disease do not normally refer to blood bank donation.

In Markazi Province, Iran the prevalence of HBV and HCV is estimated to be 0.5-1% and 0.16-0.32%, respectively. In this province with 1.5 million populations, it is estimated that 7500-15000 chronic HBV and 2250-4500 chronic HCV individuals live, respectively. This study examines the most recent epidemiological trends of HCC in HBV and HCV chronic carriers and either associated risk factors such as obesity, diabetes and alcoholism in Iran.

Materials and Methods

We present a cross-sectional study in which chronic carriers of HBV and HCV were randomly selected from a list of cases available at Arak Health Center and Blood Bank of Markazi Province, Iran (1985-2003). Selected cases were called and informed about the study design. For each patient a consent form was completed. Patients, who refused to participate, were randomly replaced by other carriers. Two trained general practitioners interviewed the enrolled cases. For each case a questionnaire was filled in order to collect data about demographic, past medical history, clinical examination of present health condition especially liver disease.

A sample of venous blood was taken from all patients for determining CBC, LFT, serum albumin, PT, alpha-feto protein (AFP), blood sugar and lipid profile. All patients underwent sonography in order to detect liver architecture, solid mass, portal vein diameter and spleen condition. Patients with AFP higher than 20 ng/ml and mass on sonography were considered to have a liver carcinoma. These cases were rechecked and underwent liver biopsy guided by sonography. We also followed up the cases after the recruitments, in terms of measuring AFP, LFT and sonographic mass every 6 months for two consecutive years.

We considered HCC as positive if patients had sonographic mass, confirmed by pathological needle biopsy documentation. We estimated duration of viral infection by the duration of the date of the first report of positive result until the time of study. The study design was approved by the ethics committee of Arak University of Medical Sciences. SPSS 13 software was used for statistical analysis. P values less than 0.05 were considered significant.

Results

Out of 1054 registered chronic carriers of HBV and HCV, 514 were randomly selected according to the registration raster. Mean age of study group was 35.19±3.16 years while in HCC patients, it was 54.2±13.16 years and the mean duration of virus carriage was 6.12±5.66 years according to the date of the first laboratory report. In HCC group, 14 individuals (87.5%) had had the virus for more than 15 years.

Of 514 patients 384 (74.7%) were males and 130 (25.2%) were females. There was no association between type of virus and HCC (P=0.3). In this study, 18 (3.5%) had liver mass of more than 1 cm on sonography, 29 (5.7%) had AFP>20 ng/ml and 16 (3.1%) had HCC, pathologically. Out of 16 cases of HCC, 12 were diagnosed during the 2 years of follow up. So the estimated annual incidence of HCC was 1.02 (95% CI: 0.5-1.8). Table 1 represents some of the para-clinical findings among the cases. Of 514 cases, 31 (6.03%) had a history of alcohol consumption, 102 (19.8) had a history of IV drug abuse and opium addiction. Table 2 compares a number of para-clinical and demographic factors in HCC and non-HCC groups.

Discussion

Our study showed the prevalence of HCC was about 3.1% in HBV and HCV chronic carriers.

Table 1. Different para-clinical findings in HBV and HCV chronic carriers.

Clinical & para-clinical factors	Abnormal findings (%)
HBV +	331 (64.4)
HCV +	146 (28.4)
HBV + & HCV +	37 (7.2)
HBeAg +	26 (5.5)
Liver cirrhosis	54 (10.3)
* Metabolic disease	24 (4.7)
Ascites	49 (9.6)
ALT >40 IU	115 (22.4)
Spider angioma	17 (18)
Splenomegaly	61 (11.9)

* Metabolic disease includes hypothyroidism, diabetes and dyslipidemia.

Table 2. Comparison of demographic, clinical and lab findings between HCC and non-HCC groups.

Risk factors	HCC group (n=16)	Non-HCC group (n = 498)	OR (95% CI)	P Value
Female sex	37.5%	24.9%	0.55 (0.19-1.55)	0.25
Age < 40 years	6.3%	67.5%	0.55 (0.97-1.55)	< 0.001
Metabolic disease	12.5%	4.4%	3.08 (0.66-14.42)	0.17
HBeAg +	25%	9.7%	3.12 (0.97-10.05)	0.07

This is about 1,000 times grater than Iranian general population among whom the prevalence is reported as 3/100,000 [17, 18]. A limitation of our study was its lack of the possibility to generalize the results to the populations of HBV and HCV infected patients, since the samples were selected only from those who were volunteers for blood donation.

Viral Hepatitis is known to be one of the most common causes of HCC in the world [1-5]. Our study indicated that HBV infection was less common in Iran than that in Southeast Asia and Africa [4, 5, 7]. The prevalence of HBV and HCV infections increases in young adults due to the steady increase in the IV drug abuse in young adults together with other high-risk habits [5]. In the present study we found that most of HCC cases were HBV positive which seems to be because of higher prevalence and longer duration of HBV infection [5]. In contrast with other studies, HBeAg positivity was not statistically significant, which may be as a result of our small sample size [4].

Habitual factors such as alcohol consumption are less common in this study group as expected in our country. In contrast, in Europe and North America, chronic alcoholism accounts for 75% of HCC cases [4], while in East Asia and Africa chronic HBV accounts for more than 85% of HCC cases [5, 10]. Mean age of our HCC cases was about 54.2 years; it seems that the age of HCC cases has shifted toward the younger age in Markazi Province, and is similar to the reports of other countries [4, 5, 7, 9].

According to our study, there was no association between type of viruses and HCC. In South Asia and Africa it has been shown that HBV infection is the main cause of HCC [1, 5, 7]. In contrast, in Western countries alcoholism and HCV play greater role for HCC [5]. In our cases, metabolic diseases such as dyslipidemia, hypothyroidism and diabetes were not significantly associated with HCC. This is in contrast with a number of studies [5, 14] which is due to our case selection; because in our study, samples were selected from HBV and HCV chronic carriers.

In conclusion, our study showed that HCC in our country is less common than that in East Asia and South Africa but we are still similar to them in term of the main risk factors. HBV and HCV chronic infections are the most common causes of HCC. However, in Western countries alcoholism remains the most common cause.

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