Is There Any Association Between Blood Groups And Hepatocellular Carcinoma (HCC)?: A Preliminary Study

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Abstract

The study conducted on randomly selected 54 patients: 38 patients with hepatocellular carcinoma (HCC); 16 patients with cirrhosis and 10 healthy volunteers during the period of December 2001 to June 2002. 10 ml blood from each patient and control were collected. Each sample was divided into two parts: 1) 2 ml freshly used blood on ethylene – diamine – tetracetic acid (EDTA) as a preservative for testing the following blood group antigens by agglutination technique: Major blood groups [ABO and RhD] and Minor blood groups [Rhd, MNSs, Duffy (Fy) and Lewis (Le)]. 2) The sera of the remaining blood samples (8 ml) were used to diagnose HCC patients: Two hepatitis markers: p53 autoantibodies (p53 Abs) and vascular endothelial growth factor (VEGF). The results reveal that, no significant correlation is found between any of the studied blood group systems and HCC or cirrhosis. Also, no significant correlation is found between any of the studied blood group systems and VEGF and p53 markers except the significant correlation between M blood group and VEGF ($p = 0.02$).

INTRODUCTION

Hepatocellular carcinoma (HCC) is among the most common cancers in the world. It accounts for up to 85 % of primary liver cancers. The tumor is linked to environmental, dietary and lifestyle factors, so that its incidence and distribution vary widely among ethnic groups, geographical regions and sex (Gelatti et al., 2003).

In 1990, more than 400,000 new cases of HCC became apparent worldwide, accounting for 5.4 % of all human cases of cancer and affecting men more than women (7.4 % and 3.2 %, respectively). In terms of relative frequency, HCC ranks as the fifth most common cancer in the world and the second most common cancer of the digestive tract, after cancer of the stomach (Sherman and Klein, 2004). Geographic regions are categorized based on the incidence of HCC as areas of low incidence (< 3 cases / 100.000 men), intermediate incidence (between 3 and 30 cases) and high incidence (> 30 cases) (Bosch et al., 2004).

The highest age incidence rates of HCC are in eastern Asia and central and western Africa where the incidence of HCC ranges from 22 to 35 / 100.000 men. A trend towards higher incidence rates of HCC has been documented in several developed countries, mainly as a result of increased population exposure to environmental risk factors and a decline in serious illnesses that compete with HCC as a cause of mortality (Colombo, 1999). The number of HCC cases has increased in the U.S. during the past two decades. The incidence raised from 1.4 / 100.000 persons during the period from 1976 to 1980 to 2.4 / 100.000 during the period from 1991 to 1995 with a shift in the incidence rate towards younger age groups (Camma et al., 2001).

The annual incidence of HCC in patients with compensated cirrhosis is about 3 % and HCC has been identified as a relevant cause of death in these patients (Loof et al., 1994). Once cirrhosis is established the main predictor of tumor are male sex, increased serum levels of alpha fetoprotein (AFP), severe disease and a high rate of liver cell proliferation. The risk for HCC is high in cirrhotic patients with typical macroregenerative nodules (Howel et al., 1999).

Blood groups are one of the most conventional genetic markers of the blood. There are six red blood cells antigens systems named (ABO, Rh, MNSs, Kell, Duffy and Kidd). However, there are many other antigenic markers in human blood that stimulate the production of antibodies in recipients of blood transfusion (Calhoun and Petz, 2001).

Each blood group system is a series of red cell antigens, determined either by a single genetic locus or very closely linked loci. Alternative forms of genes coding for red cell antigens at a particular locus are called “alleles” and individuals may inherit identical or non – identical alleles.

Most of blood group genes have been assigned to specific chromosomes (Daniels et al., 1995).

Researches revealed relationship between blood groups and some diseases. Imai et al. (1985), stated that individuals with primary hepatoma showed higher levels of antigen O concentration than normal control group. Several cases with gall bladder, lung and pancreatic carcinomas which are of O blood group type also had higher levels of this antigen. These data suggested that the release or shedding of the antigen from the cells was increased due to malignant transformation, resulting in higher amounts of the antigen in the serum of certain cancer patients.

The aim of the present work is to find out if there is any association between blood group antigens; [Major blood groups [ABO and RhD] and Minor blood groups [Rhd, MNSs, Duffy (Fy) and Lewis (Le)] and HCC patients.

SUBJECTS & METHODS

The study included randomly selected 54 patients admitted to Gastroenterology Surgery Center, Mansoura University, Mansoura, Egypt during the period of December 2001 to June 2002. The patients were: 38 patients with hepatocellular carcinoma (29 males & 9 females); 16 patients with cirrhosis (positive control group i.e. cirrhosis is an important underlying cause of HCC) (12 males & 4 females) and 10 healthy volunteers (negative controls) (7 males & 3 females). 10 ml blood from each patient and control were collected. Each sample was divided into two parts:

1) 2 ml freshly used blood on ethylene – diamine – tetracetic acid (EDTA) as preservative for testing the following blood group antigens by agglutination technique: Major blood groups [ABO and RhD] and Minor blood groups [Rhd, MNSs, Duffy (Fy) and Lewis (Le)] (38 patients with HCC, 16 patients with cirrhosis and 10 healthy volunteers) according to the method of Bethesda (1993).

2) The sera of the remaining blood samples (8 ml) were used to diagnose HCC patients: Two hepatitis markers: 1- p53 autoantibodies (p53 Abs) according to the method of Engvall and Perlman (1971); 2- vascular endothelial growth factor (VEGF) according to the method of Modified Engvall and Perlman (1971).

STATISTICAL ANALYSIS

The results were computed on IBM PC microprocessor by the statistical analysis program package, GraphPad Instat, copyright © 1990-1993 GraphPad Software, Version 2.03, USA. Data were presented as number and frequency (%). Comparisons between two independent groups were performed by the Mann-Whitney U test for two nonparametric tests. The Ranked-Spearman correlation test (r) was done to study the relation between the studied parameters. Values of $p < 0.05$ were considered significant.

RESULTS

Table (1) shows the phenotypes numbers and frequencies of ABO, Rh, MNSs, Duffy (Fy) and Lewis (Le) blood group systems in both HCC and cirrhotic patients and healthy volunteers.

ABO system: A_1 was the predominant (22 cases), followed by O (16 cases), B (14 cases) and lastly the A_1B (12 cases).

Rh system: Most of cases were Rh positive (60 cases), while the remaining 4 cases were Rh negative.

- MNSs system: The MNSs was detected in 30 cases, followed by the MMSs in 12 cases, NNSs in 11 cases, MNss in 4 cases, MMss in 3 cases, and lastly MNSs and NNss (2 cases each), while NNSS and MMSS was not detected in the studied sample (zero).

Duffy system: Fy (a + b +) was 46 cases, followed by Fy (a – b+) 16 cases, Fy (a + b -) 2 cases and lastly Fy (a – b -) zero.

Lewis system: Le (a + b +) was 51 cases, followed by Le (a – b +) 11 cases, Le (a + b -) 2 cases and lastly Le (a - b -) zero.

The correlation between blood groups and patients with HCC and cirrhosis is studied as shown in tables 2 & 3. The results reveal that, no significant correlation is found between any of the studied blood group systems and HCC or cirrhosis.

The correlation between blood groups and the two hepatitis markers (p53 & VEGF) are shown in tables 4 & 5. The results reveal that, no significant correlation is found between any of the studied blood group systems and VEGF and p53 markers except the significant correlation between M blood group and VEGF ($p = 0.02$).

Figure 1

Table 1: The phenotypes frequencies of the studied blood group systems in .

Blood groups / Studied group		Healthy volunteers (n = 10) n (%)	Cirrhotic group (n = 16) n (%)	HCC group (n = 38) n (%)
A	A_1	5 (50 %)	8 (50 %)	9 (23.68 %)
	A_2	0 (0 %)	0 (0 %)	0 (0 %)
B	-	2 (20 %)	3 (18.75 %)	9 (23.68 %)
AB	A_1B	1 (10 %)	1 (6.25 %)	10 (26.32 %)
	A_2B	0 (0 %)	0 (0 %)	0 (0 %)
O	-	2 (20 %)	4 (25 %)	10 (26.32 %)
Rh - D (Rh + ve)		9 (90 %)	15 (93.75 %)	36 (94.74 %)
Rh – d (Rh – ve)		1 (10 %)	1 (6.25 %)	2 (5.26 %)
MNSs		7 (70 %)	7 (43.75 %)	16 (42.11 %)
MNSS		0 (0 %)	2 (12.5 %)	0 (0 %)
MNss		0 (0 %)	2 (12.5 %)	2 (5.26 %)
NNSs		0 (0 %)	2 (12.5 %)	9 (23.68 %)
NNSS		0 (0 %)	0 (0 %)	0 (0 %)
NNss		0 (0 %)	0 (0 %)	2 (5.26 %)
MMSs		3 (30)	1 (6.25 %)	8 (21.06 %)
MMSS		0 (0 %)	0 (0 %)	0 (0 %)
MMss		0 (0 %)	2 (12.5 %)	1 (2.63 %)
Fy (a + b -)		0 (0 %)	1 (6.25 %)	1 (2.63 %)
Fy (a + b +)		6 (60 %)	10 (62.5 %)	30 (78.95 %)
Fy (a - b +)		4 (40 %)	5 (31.25 %)	7 (18.42 %)
Fy (a - b -)		0 (0 %)	0 (0 %)	0 (0 %)
Le (a + b -)		0 (0 %)	0 (0 %)	2 (5.26 %)
Le (a + b+)		7 (70 %)	13 (81.25 %)	31 (81.58 %)
Le (a - b +)		3 (30 %)	3 (18.75 %)	5 (13.16 %)
Le (a - b -)		0 (0 %)	0 (0 %)	0 (0 %)

Figure 2

Table 2: Correlation between blood groups of HCC patients (n = 38).

Blood groups	Correlation coefficient (r)	p Value
ABO		
A_1	0.009	0.952
A_2B	-0.248	0.090
O	0.043	0.772
B	-0.243	0.096
Rh		
Rh +	0.044	0.764
Duffy (Fy)		
Fy a	0.082	0.580
Fy b	0.044	0.764
Fy ab	0.098	0.509
Lewis (Le)		
Le a	-0.019	0.898
Le b	0	0
Le ab	-0.019	0.898
MN		
M	-0.171	0.246
N	0.082	0.580
MN	-0.061	0.683
S		
SS	0.142	0.334
Ss	0.258	0.077
ss	0.269	0.064

***p < 0.05 is significant.**

Figure 3

Table 3: Correlation between blood groups of patients with cirrhosis (n = 16).

Blood groups	Correlation coefficient (r)	p Value
ABO		
A_1	0.009	0.952
A_2B	-0.248	0.090
O	0.043	0.772
B	-0.243	0.096
Rh		
Rh +	-0.044	0.764
Duffy (Fy)		
Fy a	-0.082	0.580
Fy b	-0.044	0.764
Fy ab	-0.098	0.509
Lewis (Le)		
Le a	0.019	0.898
Le b	0	0
Le ab	0.019	0.898
MN		
M	0.171	0.246
N	-0.082	0.580
MN	0.061	0.683
S		
SS	-0.142	0.334
Ss	-0.258	0.077
ss	-0.269	0.064

p < 0.05 is significant.

Figure 4

Table 4: Correlation between patients blood groups and VEGF.

Blood groups	Correlation coefficient (r)	p Value
ABO		
A_1	0.119	0.475
A_2B	-0.016	0.925
O	-0.298	0.069
B	0.136	0.416
Rh		
Rh +	0	0
Duffy (Fy)		
Fy a	-0.077	0.647
Fy b	0.257	0.119
Fy ab	0.048	0.777
Lewis (Le)		
Le a	-0.152	0.364
Le b	0	0
Le ab	-0.152	0.364
MN		
M	0.372	0.022*
N	-0.201	0.226
MN	0.141	0.398
S		
SS	-0.152	0.364
Ss	-0.064	0.703
ss	-0.169	0.312

*p < 0.05 is significant.

Figure 5

Table 5: Correlation between patients blood groups and p53.

Blood groups	Correlation coefficient (r)	p Value
ABO		
A_1	-0.060	0.689
A_2B	-0.084	0.572
O	0.183	0.219
B	0.174	0.243
Rh		
$Rh+$	0.138	0.354
Duffy (Fy)		
$Fy\ a$	0.103	0.489
$Fy\ b$	0.198	0.183
$Fy\ ab$	0.185	0.213
Lewis (Le)		
$Le\ a$	0.084	0.572
$Le\ b$	0	0
$Le\ ab$	0.084	0.572
MN		
M	0.023	0.878
N	0.103	0.489
MN	0.111	0.458
S		
SS	0.047	0.753
Ss	0.198	0.183
ss	0.153	0.305

*$p < 0.05$ is significant.

DISCUSSION

The blood group antigens are stable characteristics controlled by genes inherited in a simple Mendelian manner (Huang et al., 1991). The frequencies of the major blood groups: (ABO and rhesus {Rh} and some of the minor blood groups (Duffy {Fy}, Lewis {Le} and MNSs are studied in 38 patients with HCC, 16 patients with cirrhosis and 10 healthy volunteers. This is a preliminary study which done on small number of available patients because of the short duration of the study.

Okada et al. (1987) had studied the expression of blood groups ABH and Lewis a and b antigens in HCC patients. HCC in some cases expressed H and Le b antigens. Kanai et al. (1987) studied the expression of Le blood group in 20 HCC patients. They found that (Le y) antigen was detected in some cirrhotic patients. While Le x and Le y antigens were detected in 30 % of HCC patients. Le a and Le b antigens were not detected in non cancerous hepatocytes and rarely detected in HCC. The results suggested that Le a and Le b antigens were useful markers for differentiation between biliary epithelial cells in liver while Le x and Le y antigens expressions might be associated with states of increased or altered cells proliferation.

Also in (1989), Jovanovic et al., had studied the distribution of Le x and Le y antigens in 26 HCC patients. They reported that Le x antigen was expressed infrequently (8 %), while Le y antigen was detected in 31 % of cases.

In addition, Wakabayashiet et al. (1995) observed the altered expression of Le blood group antigen during malignant transformation and this can be used clinically as tumor marker of a prognostic indication. The authors examined the association between Le y antigen expression and clinico - pathologic features of HCC. The results showed that Le y antigen was detected on the membrane and cytoplasm of cancer cells of 46 HCC cases, 20 expressed Le y antigens in the tumor cells. There was no correlation between Le y antigen expression and the stage of tumor. However the incidence of Le y antigen positive cases in poorly differentiated HCC was found to be significantly higher than that in moderately differentiated HCC.

Lin (1992), studied five monocolonal antibodies which recognized A, B, H and (Le a and b) blood group antigens collected from 40 cases of HCC and 63 cases of chronic hepatitis. The results mentioned that five blood group antigens were highly expressed in 11 hepatitis cases and in 19 HCC cases.

Trevisani et al. (1993) studied the prevalence of different hepatocellular carcinoma and association between these types and blood groups and the underlying cirrhosis and cancer in 416 patients. The results revealed that cirrhosis and blood groups other than O were independent risk factors for HCC. i. e. there was a positive association between HCC and blood group O.

The results of the present study are in contrast to the previous studies as there is no association was detected between any of the studied blood groups and HCC or cirrhosis. On the other hand, only association is detected between “M” blood group antigen and one of the studied HCC markers (VEGF) ($p = 0.02$). To our knowledge no other previous studies have shown any correlation between HCC marker (VEGF) and MN blood group.

On the other hand the results of the present study are in accordance to the results of the study of Neukirchen and Haase (1981). They found that there was no significant association between ABO blood group antigens in alcoholic patients and liver damage patients.

Stigendal et al. (1984) had studied the distribution of ABO, rhesus and Lewis antigens in patients with alcoholic cirrhosis, alcoholic pancreatitis, chronic liver hepatitis and primary biliary cirrhosis. They found no differences in the frequencies of ABO and rhesus between the studied groups while patients with alcoholic cirrhosis and alcoholic pancreatitis showed negative Lewis antigens (Le a – b -).

From the results of the present study and previous studies concerning the association between different blood groups and HCC, it can be concluded that no significant correlation was detected. These results suggested that no specific blood group could be considered as a risk factor for the occurrence of HCC in the studied patients. In the future more researches are required to be performed on larger number of patients in a trial to reach to a more statistical conclusive data.

It is recommended in the future studies to determine MN antigens in every patient with a history of liver disease especially the cirrhotic patients. Also, testing other minor blood groups as Kell (K), Kidd (Jk), Ii and P for possibility of association with HCC or cirrhotic patients.

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