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Full Length Research Paper

Etiology of hepatitis G virus (HGV) and hepatitis type C virus (HCV) infections in non-Hodgkin's lymphoma patients in Southern Iran

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Hepatitis G virus (HGV) and hepatitis type C virus (HCV) may implicate malignant lymphoma including non-Hodgkin's lymphoma (NHL) for inducing the proliferative process of lymphocytes. In this study, the molecular and serologic prevalence of HGV and HCV infections was evaluated in patients with NHL and compared with the controls. In this cross sectional study, ethylene diamine-tetra acetic acid (EDTA)-treated blood samples were collected from 140 patients with NHL and 120 healthy controls from 2007 to 2011 years. The serological markers of HCV and HGV viruses were evaluated in both studied groups by enzyme linked immunosorbent assay (ELISA) methods. Also, the HGV and HCV viremia was analyzed in patients with NHL and control group by reverse transcriptase (RT)-PCR protocols. Anti-E2-Ab was detected in 5 of 140 (3.6%) NHL patients. HGV-RNA was diagnosed in 6 of the 140 (4.3%) studied patients. HGV-RNA was diagnosed in 3 of the 120 (2.5%) controls. HCV-RNA was diagnosed in 22 of the 140 (15.7%) patients with NHL. Also, significant difference was detected in the prevalence of HCV genome between NHL and the controls. Significant differences were not found in serologic and molecular prevalence of HGV between NHL and the controls. Determination of the active and persistent infections of HGV in patients with NHL compared with the controls and also identification of higher significant prevalence of HCV infection in patients with NHL proposed strong association between HCV infection and NHL pathogenesis.

Key words: Hepatitis G virus (HGV), hepatitis type C virus (HCV), non-Hodgkin's lymphoma (NHL).

INTRODUCTION

Hepatitis G virus (HGV) is a lymphotropic RNA virus similar with the other member of the Flaviviridae family, hepatitis type C virus (HCV), in genome organization and structure. HGV infection may not have been the direct cause of any specific disease but may have induced solely or concomitant with HCV malignant lymphoma including non-Hodgkin's lymphoma (NHL) (Polgreen et al., 2003). As noted earlier, 10 to 20% of HCV-infected individuals are co-infected with HGV. In some earlier studies, the rates and severity of clinical liver disease among people with HGV and HCV co-infection were presented (Alter, 1997a, Alter et al., 1997b; Fried et al., 1997; Masuko et al., 1996; Rambusch et al., 1998; Tanaka et al., 1996; Tillmann et al., 1998). The pathogenesis of HGV and HCV is characterized by proliferation in peripheral blood mononuclear lymphocytes (Franceschi and De Martel, 2009; Engels et

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Abbreviations: HGV, Hepatitis G virus; **HCV,** hepatitis type C virus; **NHL,** non-Hodgkin's lymphoma; **EDTA,** ethylene diamine-tetra acetic acid; **ELISA,** enzyme linked immunosorbent assay; **RT-PCR,** reverse transcriptase polymerase chain reaction.

al., 2004; Mostafa et al., 2003). HGV and HCV may induce the aberrant immunologic response and probably have a role in introducing or complicating the outcome of NHL (Engels, 2007; Zignego et al., 2007). Also, HGV and HCV may have prolonged stimulation on the immune system which may increase the rates of lymphoma (Engels, 2007; Levrero, 2006). It is hypothesized that a specific stimulation of B cells to lymphotropic viruses may lead to uncontrolled proliferation of lymphocytes (Mazzaro et al., 2005). Earlier reports from different geographic areas presented an association between HGV and pathogenesis of NHL. The higher prevalence of HGV genome has been found in patients with NHL compared to controls (Ellenrieder et al., 1998; Giannoulis et al., 2004; De Renzo et al., 2002; Kaya et al., 2002; Minton et al., 1998; Pavlova et al., 1999; Zignego et al., 1997). But some studies with limitations in sample size and related controls have not found an association between HGV infection and NHL (Arican et al., 2000; Collier et al., 1999; Keenan et al., 1997; Michaelis et al., 2003; Nakamura et al., 1997). On the other hand, HCV appears to have a role in the pathogenesis of a proportion of patients with NHL (Franceschi et al., 2009; Engels, 2007). Association between HCV and NHL was supposed lately and has been the subject of high investigations as well as some arguments (Engels et al., 2004; Zignego et al., 2007; Dogan and Viswanatha, 2007). HCV infection is thought to promote the NHL development by inducing chronic lymphoproliferation through persistent antigenic stimulation (Franceschi et al., 2009; Engels, 2007; Mehdi and Al Ajlan, 2006). Several reports, mainly from Asia and Europe (Alter et al., 1997b; Engels et al., 2004; Mostafa et al., 2003; Al-Ghiti et al., 2006; Iannitto et al., 2002; Park et al., 2008; Wu et al., 2006), have shown an increase in the prevalence of HCV infection in B-cell NHL patients (Franceschi et al., 2009; Engels et al., 2004; Zignego et al., 2007; Al-Ghiti et al., 2006; Iannitto et al., 2002; Park et al., 2008; Wu et al., 2006). Based on these findings, HGV and HCV single and co-infection may increase the risk of NHL. Therefore, in this study the possible association between HGV and HCV infections with etiology of NHL was evaluated.

MATERIALS AND METHODS

All patients with NHL were enrolled in this study; they were admitted from different geographical regions of Southern Iran to Namazee Hospital of Shiraz University of Medical Sciences, Shiraz, Iran, between 2007 and 2011 years. Identification and classification of NHL malignancies were evaluated by expert pathologists and hematooncologists based on WHO criteria. The control group included hospital patients who were clinically ruled out of hematological malignancies and abnormalities in the laboratory. EDTA treated blood samples were collected from 140 NHL patients and 120 healthy control group. Also, some risk factors of NHL pathogenesis were statistically analyzed for all studied patients with NHL.

HGV and HCV antigenic and serological analysis

Antibody against HGV-E2 glycoprotein (Anti-E2 Ab) was evaluated in plasma samples by third generation ELISA kit (DIAPRO, Italy), according to the manufacturers' instruction. Anti-HCV antibody (HCVAb) was analyzed in studied plasma samples by third generation ELISA kit (DIAPRO, Italy), according to the manufacturers' instruction.

HGV and HCV molecular diagnosis

HCV-RNA extraction and amplification

The HCV-RNA genome was extracted from plasma samples by RNA plus extraction procedure as previously described (Ebadi et al., 2011). The quality of extraction technique was evaluated by spiking of HCV-RNA in HCV negative plasma sample. The extracted HCV-RNA was amplified by a qualitative Nested-HCV-RT-PCR detection Kit (CinnaGen, Iran), according to the manufacturers' instruction.

HGV-RNA extraction and amplification

HGV genome was also extracted by RNX-plus extraction procedure as previously described (Ebadi et al., 2011). The presence of HGV -RNA genome was analyzed by an in-house Nested-HGV-RT-PCR protocol. In the RT-PCR step cDNA was synthesized from 3 µl extracted HGV RNA at 25°C for 1 h and at 72°C for 10 min using random hexamer and Moloney murine leukemia virus reverse transcriptase (M-Mulv-RT). The 20µL RT-master mix contained 0.2 mMol of dNTPs, 0.01 mg/ml of Random Hexamer, 7.5 U/ml of M-Mulv-RT, 1 U/ml of ribonuclease inhibitor, and 4 µl of 5 µl RT-buffers.

In the simple PCR protocol, the PCR master mix contained: 2 µl of cDNA, 0.1 pMol/µl of primers, 0.2 mMol of dNTPs, 2.5 U of Taq DNA polymerase, 2.5 µl of 10X PCR buffer, and 1.5 mMol of $MgCl_2$. The 2 µl of simple PCR product was used in second round of nested PCR step with the same condition as simple PCR protocol. The total volume per reaction in two rounds of simple and nested PCR protocols was 25 µl. The thermocycling conditions for simple and nested PCR rounds were the same. Simple PCR was initiated with a first round at 95°C for 5 min followed by a second round of 25 cycles at 94°C for 50 s, 55°C for 40 s, and 72°C for 50 s, and finalized with extension at 72°C for 3 min. The nested PCR protocol was initiated with a first round at 95°C for 5 min followed by a second round of 35 cycles at 94°C for 40 s, 64°C for 35 s and 72°C for 40 s, and finalized with extension at 72°C for 3 min.

Statistical analysis

Significant differences between serologic and molecular diagnostic markers of HGV and HCV in patients with NHL and controls and also statistical correlations between viral hepatitis infective markers in patients and controls were analyzed by parametric and non parametric analyses with SPSS for Windows (version 12, Chicago, IL, USA). A level of $P \leq 0.05$ was accepted as statistically significant.

RESULTS

The 80 of 140 (57%) patients with NHL are males and 60 of 140 (43%) of patients were females with mean age of 43 ± 16.98 years old. Also, 42 of 120 (35%) controls were males and the rest of them, 78 of 100 (65%) were

Table 1. Prevalence of HGV and HCV infective markers in NHL patients and controls.

Marker	NHL patients number (%)	Control group number (%)	P-value	OR	95% CI
HCV Ab					
-Ve	136/140 (97.1)	120/120 (100)	0.015	0.943	0.890-0.999
+Ve	4/140 (2.9)	0/120 (0)			
HGV Ab					
-Ve	135/140 (96.4)	120/120 (100)	0.342	0.756	0.865-1.234
+Ve	5/140 (3.6)	0/120 (0)			
HGV-RNA					
-Ve	134/140 (95.7)	117/120 (97.5)	0.258	0.432	0.028-3.453
+Ve	6/140 (4.3)	3/120 (2.5)			
HCV-RNA					
-Ve	118/140 (84.3)	120/120 (100)	0.0001	0.857	0.779-0.943
+Ve	22/140 (15.7)	0/120 (0)			

+Ve: Positive; -Ve: negative; NV: not valid.

females with mean age of 36 ± 12.87 years old. All patients with NHL and controls were adults. B-cell NHL is the most prevalent type of lymphoma in the studied patients.

Molecular presentation of HGV and HCV

HGV-RNA was diagnosed in 6 of 140 (4.3%) patients with NHL and one of them also showed the history of HBV infection. HGV-RNA was diagnosed in 3 of 120 (2.5%) controls. No Significant difference was found in the prevalence of HGV genome between NHL and the controls. On the other hand, HCV-RNA was diagnosed in 22 of 140 (15.7%) patients with NHL and none of healthy controls. Also significant difference was detected in prevalence of HCV genome between patients with NHL and controls (P=0. 0001; OR=0.857; 95%CI=0.779 - 0.943) (Table 1).

Serological presentation of HGV and HCV

Anti-E2- HGVAb was found in 5 of the 140 (3.6%) NHL patients and none were found in the controls. HCVAb was found in 4 of 140 (2.9%) NHL patients and none was found in the controls. Patients with NHL simultaneously presented HCV genome in related plasma sample (Tables 1 and 2). Significant difference was found in the prevalence of HCV antibody between NHL and controls (P = 0.015; OR = 0.943; 95%CI = 0.890-0.999) (Table 1).

Single and multiple infections of HGV and HCV

At least one of the different molecular and immunological markers of HGV and HCV was found in 7 of 140 (5%), and 22 of 140 (15.7%) patients with NHL, respectively. Also HGV and HCV infective markers were found in 3 of 120 (2.5%), and none of controls, respectively. Co-infection of HGV and HCV was diagnosed by evaluation of different markers of these two viruses in 3 of 140 (2.1%) patients with NHL. Co-infection of HGV with HCV was not diagnosed in any of the controls.

HGV and HCV and risk factors of NHL

Significant relationship was found between anti-E2 HGVAb with types of lymphoma (P=0.046). HGV-RNA was significantly correlated with age (P=0.012). History of smoking (P=0.018) had significant correlation with HCV infection. But significant correlations were not seen between other risk factors with HGV and HCV infective markers.

DISCUSSION

Viral hepatitis infections have variable presentation in patients with NHL and associate with a wide spectrum of liver involvement (Franceschi et al., 2009; Engels et al., 2004; Engels, 2007; Mostafa et al., 2003). With some controversy, hepatitis viruses HGV can infect and propagate in lymphoid cells and tissues and has the potential to participate in the malignancy of lymphoid tissues like NHL (Kim et al., 2002; Rambusch et al., 1998; Kaya et al., 2002; Pavlova et al., 1999; Arican et al., 2000; Collier et al., 1999; Krajden et al., 2010). Earlier studies with some limitations also support this hypothesis. HGV viremia was found in 4.5% of NHL cases vs. 1.8% of controls. Also they found strong association between HGV viremia with diffuse large B cell

Table 2. Frequencies and average values of indices in patients with NHL and controls.

Indices population of study	Age (Mean+-SD)	Gender N (%)		HGV-RNA	HGV-Ab	HCV-RNA	HCV-Ab
		Male	Female	N (%)	N (%)	N (%)	N (%)
Patients with NHL	43±16.98	80 of 140 (57)	60 of 140 (43)	6 of 140 (4.3)	5 of 140 (3.6)	22 of 140 (15.7)	4 of 140 (2.9)
Controls	36±12.87	42 of 120 (35)	78 of 120 (65)	3 of 120 (2.5)	Not detected	Not detected	Not detected

lymphoma (Krajden et al., 2010). The genome of HGV was significantly diagnosed with higher prevalence (P = 0.02) in cases with hematological malignancy (72%) than in the patients with clonally stem cell diseases (28%) (Pavlova et al., 1999).

In UK, HGV RNA was found in 10% of lymphoma patients vs. only 1% of blood donors (Minton et al., 1998). Also, they evaluated the HGV viremia in NHL cases. This group found the genome of HGV without co-infection with HCV RNA in 13% of patients with NHL. But in another study, HCV RNA was only detected in 4.3% of these lymphoma cases (Ellenrieder et al., 1998). In Turkey, HGV genome was diagnosed in 1.25%, HBsAg in 5%, and HCVAb in 1.25% of 80 patients with hematologic malignancy. HGV RNA was found in 10 of 108 (9.6%) patients with B cell NHL. But only 4 of 285 (0.7%) Greek blood donors were infected with HGV genome. The higher prevalence of HGV infection in patients with NHL could propose the potential participation of this viral infection in the pathogenesis of NHL (Giannoulis et al., 2004).

In controversial reports which benefit association between HGV infection and NHL outcomes, detection of HGV in 5% of lymphoma patients and 3% of controls emphasizes the unimportant role of HGV infection in the pathogenesis of NHL (Collier et al., 1999). Also, HGV infection was found in 7.1% of patients with NHL vs. 1.4% of controls, whose ages and sexes matched (Kaya et al., 2002). HGV infection was not detected in any patients with NHL (Arican et al., 2000). Moreover, similar to these conflicting reports, in this study anti-HGV E2-Ab was found in 3.6% of patients with NHL who have no history of HBV and HCV infections. HGV RNA was diagnosed in 4.3% of NHL patients with one of them showing the history of HBV infection. No significant difference was found in the prevalence of HGV viremia between NHL patients and controls. At least, one of molecular and immunological markers of HGV was diagnosed in 5% patients with NHLs vs. 2.5% of controls. HGV viremia was significantly correlated with age (P=0.012). Also, HGV Ab was significantly related to types of lymphoma (P=0.046).

HCV can infect B lymphocytes and mediate lymphomagenesis including NHL by motivation through particular immune-related interactions (Engels et al., 2004; Engels, 2007; Zignego et al., 2007; Dogan et al., 2007; Schöllkopf et al., 2008). HCV can replicate in the initial stages of the differentiation of progenitor hematopoietic cells. The coincident cleaning of HCV and clinical remission of NHL provides strong evidence that HCV plays an inducing role of NHL development. Most earlier studies have emphasized on the high prevalence and strong association between HCV infection and NHL pathogenesis (Franceschi et al., 2009; Engels et al., 2004; Engels, 2007; Mostafa et al., 2003; Al-Ghiti et al., 2006; Iannitto et al., 2002; Kuniyoshi et al., 2001). In Italian population, HCV was found in 17.5% of patients with NHL (Mele et al., 2003). In Turkey, higher significant prevalence of HCV infection was found in 7.1% of NHL patients vs. 1% of controls (P<0.05) (Yenice et al., 2003). Also HCV was significantly found in Japanese patients (P=0.0001) with different levels of liver enzymes in the time of NHL diagnosis (Idilman et al., 2000). Also, in another study, 9 to 37% of Europeans with NHL were infected by HCV (Zignego et al., 1997). HCV infection was diagnosed with higher significant prevalence in 22% of NHL patients compared with 4.5% of the controls (Zuckerman et al., 1997). As well as earlier reports, in this study HCV viremia was significantly highly found in 15.7% of patients with NHL compared with the controls (P=0.015).

Conclusion

In this study, an association between HCV infections with pathogenesis of NHL is suggested. However, efforts should be established in studying of the prevalence rate of HGV and HCV infections in larger groups of patients and also recommend the introduction of preventive and controlling measures of HCV infection in NHL patients.

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