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Full Length Research Paper

Evaluation of GB virus C (GBV-C)/hepatitis G virus (HGV) and hepatitis type B viruses (HBV) infections in patients with non-Hodgkin's lymphoma

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GB virus C (GBV-C)/hepatitis G virus (HGV) by infecting and encourage proliferative process of the mononuclear cells, may implicate in lymphomagenesis including non-Hodgkin's lymphoma (NHL). Therefore, in this study the prevalence of GBV-C/HGV and HBV infections were evaluated in patients with NHL and controls. In a cross sectional study, blood samples were collected from 70 patients with NHL and 100 healthy controls. The infective markers of GBV-C/HGV and HBV viruses were evaluated in both studied groups by enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) protocols, respectively. Anti-E2-Ab was detected in 1.4 of 70(1%) of NHL patients who has not the history of HBV infections. HGV-RNA was diagnosed in 2 of 70 (2.9%) of NHL patients and one of them was also shown the history of HBV infection. HGV-RNA was diagnosed in 1of 100 (1%) of controls but none of them was shown seroconversion to GBV-C/ HGV. HBV-DNA was found in 8 of 70 (11.6%) of NHL patients and 2 of 100 (2%) of controls. Significant differences were found in the prevalence of: HBV-DNA (P=0.013), HBsAb (P=0.001), and HBc-IgG-Ab (P=0.002) between NHL and controls. Determination of active and persistent infections of GBV-C/ HGV with or without HBV infection in NHL patients compared with control population proposed an association between viral hepatitis infections and NHL.

Key words: Non-Hodgkin's lymphoma (NHL), GB virus C (GBV-C), hepatitis G virus (HGV).

INTRODUCTION

GB virus C (GBV-C) and hepatitis G virus (HGV) are different isolates of the same virus with homology innucleotide (86%) and amino acid (95%) sequences (Simons et al., 1995; Linnen et al., 1996; Alter et al., 1996; Polgreen et al., 2003). By itself, GBV-C/ HGV infection may has not been directly the cause of any specific disease but may has an increasing or inducing role solely or concomitant with other hepatitis viruses like hepatitis type B viruses (HBV) in outcome of malignant or non-malignant hematological disorders and lymphoma including non-Hodgkin's lymphoma (NHL) (Polgreen et al., 2003). Extrahepatic pathogenesis of GBV-C/HGV and other hepatitis viruses are characterized by an informal proliferation in peripheral blood mononuclear leukocytes, usually lymphoid cells (De Martel et al., 2009; Engels et al., 2004; Mostafa et al., 2003). GBV-C/HGV and HBV may induce the aberrant immunologic response and probably play a role in introducing or outcome complexity of NHLs (Mehdi et al., 2006; Zignego et al., 2007; Engels et al., 2007). GBV-C/HGV and HBV may prolong stimulation of the immune system which may lead to increase the rates of malignant lymphoma (Engels et al.,

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2007; Levrero et al., 2006). It is hypothesized that, a specific stimulation in B cells against viral hepatitis infection may leads to uncontrolled polyclonal and subsequent monoclonal expansion of these lymphocytes (Mazzaro et al., 2005).

Earlier reports present an association between GBV-C/HGV viremia and NHL pathogenesis (Giannoulis et al., 2004; Kaya et al., 2002; De Renzo et al., 2002; Minton et al., 1998; Zignego et al., 1997). A higher prevalence of GBV-C/HGV genome has been found in NHL cases compared with healthy controls (Pavlova et al., 1999; Ellenrieder et al., 1998; Giannoulis et al., 2004; Kaya et al., 2002; De Renzo et al., 2002; Minton et al., 1998; Zignego et al., 1997). But in some studies that limited for small sample size and lack of controls have found no association between presentation of GBV-C/HGV and NHL ((Michaelis et al., 2003; Arican et al., 2000; Keenan et al., 1997; Collier et al., 1999; Nakamura et al., 1997). On the other hand; HBV appears to have role in the pathogenesis of a proportion of patients with NHL (De Martel et al., 2009; Engels et al., 2007; Park et al., 2008). Despite the possible association between chronic infection of HBV and NHL, lesser studies have evaluated this potential link (Kim et al., 2002; Musolino et al., 1996; Marcucci et al., 2006). Some studies conducted in Asia and Europe suggest that, chronic HBV infection is 2 to 5 times more prevalent among NHL patients compared with healthy controls without NHL (De Martel et al., 2009; Kim et al., 2002; Chen et al., 2008; Lim et al., 2007). These reports showed higher prevalence of HBV infection in patients with NHLs in Romania (30.8%) and in Japan (9.6%) (Cucuianu et al., 1999; Kuniyoshi et al., 2001). Based on these findings; this hypothesis is proposed that GBV-C/HGV single and co-infection with HBV may have inducing role in development of NHL. Therefore; in this study the plausible association of GBV-C/HGV and HBV infections with pathogenesis and outcome of NHLs was evaluated.

MATERIAL AND METHODS

Patients and samples

The ethylenediaminetetraacetic acid (EDTA)-treated blood samples were collected from to studied groups including: 70 NHL patients and 100 control persons who clinically and laboratory rule out hematological malignancies and abnormalities. Also some possible risk factors of NHL including: age, gender, marriage, types of T and B-NHLs, and history of smoking, transfusion, surgery, bone marrow transplantation and HIV infection were statistically analyzed for all studied NHL patients.

GB virus C (GBV-C)/hepatitis G virus (HGV) and hepatitis viruses (HBV) antigenic and serologic analysis

Antibody against E2 glycoprotein of GBV-C/HGV (Anti-E2 Ab) was evaluated in plasma samples by third generation ELISA kit (DIAPRO, Italy), according to manufacturer instructions.

HBV antigens including: hepatitis B surface antigen (HBsAg) and hepatitis B envelope antigen (HBeAg) and HBV antibodies including: hepatitis B surface antibody (HBsAb), hepatitis B envelop antibody (HBeAb), hepatitis B core IgM antibody (HBc IgM Ab), and hepatitis B core IgG antibody (HBc IgG Ab), were analyzed in plasma samples of studied patients by third generation ELISA kits (DIAPRO, Italy), according to manufacturer instructions.

GB virus C (GBV-C)/hepatitis G virus (HGV) and hepatitis type B viruses (HBV) molecular diagnosis

Hepatitis type B viruses (HBV)-DNA extraction and amplification: In this study the HBV-DNA was extracted from plasma samples of leukemia and control group by phenol-chloroform extraction procedure as previously described (Arjmandi et al., 2011). Also, the quality of extraction protocol was evaluated by spiking of HBV- DNA in HBV negative plasma sample. The extracted HBV-DNA was identified and amplified by using specific primers covering the surface (S) genes of HBV genome according to the instruction of a qualitative HBV-PCR detection Kit (CinnaGen, Iran).

GB virus C (GBV-C)/hepatitis G virus (HGV)-RNA extraction and amplification: The genome of GBV-C/HGV was extracted from plasma samples by RNA plus extraction procedure as previously described (Ebadi et al., 2011). Also the molecular presence of GBV-C/HGV RNA genome was determined by using an in- house reverse transcriptase-polymerase chain reaction (RT-PCR) protocol as previously described (Ebadi et al., 2011).

Statistical analysis

Significant differences of serological and molecular diagnostic markers of studied GBV-C/HGV and HBV viruses between NHL patients and control group and also statistical correlations between viral hepatitis diagnostic indices and possible risk factors of NHL were analyzed by use of parametric and non parametric logistic regression methods with SPSS for Windows (version 12, Chicago, IL, USA). A level of $P \leq 0.05$ was accepted as statistically significant.

RESULTS

The 42 of 70 (60%) patients with NHL are male and 28 of 70 (40%) of patients were female. Also 39 of 100 (39%) of controls were male and the rest of them 61of 100 (61%) were female with average age of 36 years old. All NHL patients and control group were aged over 16 (>16) years old. The 60 of 70 (85.7%) studied patients suffering from B-cell NHL and rest of them (14.3%) from T-cell NHL.

Molecular presentation of GB virus C (GBV-C)/hepatitis G virus (HGV) and hepatitis type B viruses (HBV)

GBV-C/HGV-RNA was diagnosed in 2of 100 (2%) of patients with NHL and one of them was also shown the history of HBV infection. GBV-C/HGV -RNA was diagnosed in 1of 100 (1%) of controls. HBV-DNA was found in 8 of 70 (11.6%) of NHL patients and 2 of 100 (2%) of controls. No significant difference was found in

Table1. Prevalence of GBV-C/HGV and HBV infective markers in NHL patients and controls.

Markers	NHL Patients No. (%)	Control Group No. (%)	P-value	OR	95% CI
HBs Ag					
-Ve	68/70(97.1)	98/100(98)	0.546	0.694	0.095-5.047
+Ve	2/70(2.9)	2/100(2)			
HBs Ab					
-Ve	64/70(91.4)	63/100(63)	0.0001	6.265	2.471-15.879
+Ve	6/70(8.6)	37/100(37)			
HBe Ag					
-Ve	67/70(95.7)	99/100(99)	0.190	0.226	0.023-2.215
+Ve	3/70(4.3)	1/100(1)			
HBe Ab					
-Ve	66/70(94.2)	98/100(98)	0.192	0.337	0.060-1.892
+Ve	4/70(5.7)	2/100(2)			
HBc Ab(IgG)					
-Ve	52/70(74.3)	92/100(92)	0.002	0.251	0.102-0.618
+Ve	18/70(25.7)	8/100(8)			
HBc Ab(IgM)					
-Ve	70/70 (100)	99/100(99)	0.588	1.01	0.99-1.103
+Ve	0/70 (0)	1/100(1)			
HGV Ab					
-Ve	69/70(98.6)	100/100(100)	0.233	0.986	0.958-1.014
+Ve	1/70(1.4)	0/100(0)			
HGV-RNA					
-Ve	68/70(97.1)	99/100(99)	0.368	0.343	0.031-3.863
+Ve	2/70(2.9)	1/100(1)			
HBV-DNA					
-Ve	62/70(88.5)	98/100(98)	0.013	0.158	0.033-0.769
+Ve	8/70 (11.4)	2/100(2)			

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

the prevalence of HGV genome between NHL and controls. Significant difference was found in the prevalence of HBV genome between NHL and controls (P=0.013, OR= 0.158, 95%CI= 0.033-.0769) (Table1).

Serological and antigenic presentation of GB virus C (GBV-C)/hepatitis G virus (HGV) and hepatitis type B virus (HBV)

The prevalence of HBV antigens (HBsAg and HBeAg), HBV antibodies (HBsAb, HBeAb, HBc IgM Ab, and HBc IgM Ab) and also GBV-C/HGVAb in leukemia and control patients and the significant differences between them were presented in Table 1. Anti-E2-GBV-C/HGVAb was found in 1 of 70 (1.4%) of NHL patients and none of control group (Table1).

From HBV antigens, HBsAg and also HBeAg were detected in 2 of 70 (2.9%) and 3 of 70 (4.3%) of NHL patients, respectively, and in 2 of 100 (2%) and 1 of 100 (1%) of controls, respectively. Significant differences were not detected in the prevalence of any HBV antigens between two studied groups (HBsAg: P= 0.546, OR= 0.694, 95%CI= 0.095-5.047; HBeAg: P= 0.190, OR= 0.226, 95%CI= 0.023-2.215).

HBsAb was diagnosed in 6 of 700 (8.6%) of NHL patients and 37 of 100 (37%) of control group and HBcAb-IgG diagnosed in 18 of 700 (25.7%) of NHL patients and 8 of 100 (8%) of control group. HBs and HBc-IgG antibodies had significant differences in their prevalence between two evaluated groups (P= 0.001, OR= 6.265, 95%CI= 2.471-15.879; P= 0.002, OR= 6.251, 95%CI=0.102-15.618, respectively). But no significant differences were found in the prevalence of other GBVC/HGV and HBV antigens and antibodies between NHL and control patients (Table 1).

Single and co-infections of GB virus C (GBV-C)/hepatitis G virus (HGV) and hepatitis type B viruses (HBV)

At least one of different molecular and immunological markers of GBVC/HGV and HBV was found in 24 of 70

(34.3%) and 3 of 70 (4.3%), NHL patients, respectively. Also GBVC/HGV and HBV infective markers were found in 12 of 100 (12%) and 1 of 100 (1%) controls, respectively. HBsAb which may relate to anti-HBV vaccination or curing from earlier HBV infection or disease is roll out from this frequency analysis. On the other hand; the data of infection with more than one antigenic, serological and/or molecular marker of GBVC/HGV and HBV in NHL and control patients are presented in Table 2. Co-infection of GBVC/HGV with HBV was diagnosed by evaluation of different markers of these two viruses in 2 of 70 (2.9%) of patients with NHL. Co-infection of GBV-C/HGV with HBV was not diagnosed in any of control group (Table 2).

GB virus C (GBV-C)/hepatitis G virus (HGV) and hepatitis type B viruses (HBV) markers and risk factors of non-Hodgkin's lymphoma (NHL)

HGV-RNA was significantly correlated with age (P=0.017). Also significant relationship was found between GBV-C/HGVAb with types of NHL (P=0.014). From other risk factors of NHLs, significant relationships were found between gender, history of smoking with HBeAg (P= 0.02) and history of bone marrow transplantation with HBsAb (P=0.05). But significant correlations were not seen between other risk factors of NHL including: marriage, and history transfusion, surgery, and HIV infection were statistically analyzed for all studied of NHL patients with GBV-C/HGV and HBV infective markers.

DISCUSSION

The pathogenesis of NHL should be assigned to more than single cause. From multiple inducible factors of NHL, viral hepatitis infections with variable presentation in patients with NHL and association with a wide spectrum of liver involvement have an important position (De Martel et al., 2009; Engels et al., 2004; Mostafa et al., 2003; Mehdi et al., 2006; Zignego et al., 2007). GBV-C/HGV was diagnosed with varied prevalence in normal population and patients with distinct underlying diseases in different parts of the world. The presence of anti-E2 antibody against GBV-C/HGV to be 3-8% in North America, 10.9-15.3% in Europe, 4-18% in Asia, and with prevalence is higher in South Africa and in Brazil (19.5-20.3%) (Takacs et al., 2002). Also the genome of GBV-C/HGV was found in healthy blood donors of West Africa (14.2%), South Africa (10.4-12.9%), Vietnam (5.7%), Germany (4.7%) and Thailand (4.3%) [15], but low in Japan (0.6-0.9%), China (0.7-2.0%) and in the United States (0.8-1.7%) (Takacs et al., 2002).

From hepatitis viruses GBV-C/HGV for ability to infect and propagate in lymphoid cells and tissues, has the potential to participate in extrahepatic malignancies involving lymphoid tissues like NHL with some controversy (Krajden et al., 2010; Pavlova et al., 1999; Collier et al., 1999, Arican et al., 2000; Kaya et al., 2002). Earlier reports with some limitations were also support this hypothesis. In Canada GBV-C/HGV viremia was found 4.5% of NHL cases versus 1.8% of controls. Also in this study, strong association was confirmed between GBV-C/HGV viremia with diffuse large B cell lymphoma (Krajden et al., 2010). In Austria the genome of GBV-C/HGV was significantly higher in prevalence (P= 0.02) in cases with lymphoma and leukemia (72%) than in the patients with clonal stem cell diseases (28%) (Pavlova et al., 1999). Minton et al. (1998) also found GBV-C/HGV RNA in 10% of lymphoma patients versus only 1% of healthy blood donors. Ellenrieder et al. (1998) evaluated the GBV-C/HGV viremia in NHL cases. In this study, the genome of GBV-C/HGV without co-infection with HCV RNA was found in 13% of NHL patients. But HCV RNA was only detected in 4.3% of these lymphoma cases (Ellenrieder et al., 1998). Ýdýlman et al., 2000 diagnosed GBV-C/HGV genome in 1.25%, HBsAg in 5%, and HCVAb in 1.25% of 80 patients with hematologic malignancies. They present no significant increase in transmission rates of GBV-C/HGV infection in these patients (Ýdýlman et al., 2000). In Greece, 10 of 108 (9.6%) cases with B cell NHL were shown GBV-C/HGV genome in their serum. But only 4 of 285 (0.7%) of Greek blood donors were infected with GBV-C/HGV RNA. The increased prevalence of GBV-C/HGV infection in patients with NHL could propose the potential participation of this viral infection in the pathogenesis of NHL (Giannoulis et al., 2004).

Controversially, by detection of GBV-C/HGV in the serum of 5% of lymphoma patients and 3% of healthy controls, unimportant role of this viral infection in the pathogenesis of B-cell lymphoma in North America was presented (Collier et al., 1997). In turkey, 7.1% of patients with NHL vs. 1.4% of controls who age- and sex-matched were infected with GBV-C/HGV RNA, but the difference was not statistically significant (P >0.05) (Kaya et al., 2002). In other study in turkey, HGV infection was not detected in none of the patients with NHL (Arican et al., 2000). Moreover, to these conflicting reports in this study, anti-E2-Ab against GBV-C/HGV was found to be 1.4% of NHL patients who has no history of HBV and HCV infections. GBV-C/HGV RNA was diagnosed in 2% of NHL cases. GBV-C/HGV RNA was diagnosed in 1% of control group but none of these persons was shown seroconversion to GBV-C/HGV. No significant difference was found in the prevalence of HGV genome between NHL patients and controls. GBV-C/HGV genome was significantly correlated with age (P= 0.017). Also, GBV-C/HGVAb was significantly related to types of lymphoma (P= 0.014).

On the other hand, acute and chronic infection of HBV was found in nearly 500 million persons worldwide

Table 2. Non-Hodgkin lymphoma and control patients infected by more than one GBV-C/HGV and HBV markers.

Viral Hepatitis markers patients	HBs Ag	HBe Ag	HBs Ab	HBe Ab	HBc IgG Ab	HBc IgM Ab	HGV Ab	HGV RNA	HBV DNA	HBV clinical decision
NHL										
1	+	-	-	+	+	-	-	-	-	CI
2	-	+	-	-	-	-	+	-	-	CI
3	-	+	-	-	+	-	-	+	-	CI
4	-	+	-	-	+	-	-	-	-	CI
5	-	-	+	+	+	-	-	-	-	HI or CI
6	-	-	+	-	+	-	-	-	-	HI or CI
7	-	-	-	-	-	-	-	-	+	CI
8	-	-	-	-	+	-	-	+	-	HI or CI
9	-	-	+	-	-	-	-	-	+	HI or CI
10	-	+	-	-	+	-	-	-	-	HI or CI
11	-	-	-	-	+	-	-	-	+	HI or CI
12	-	-	-	+	+	-	-	-	-	HI or CI
13	-	-	+	-	+	-	-	-	+	HI or HV
14	-	-	-	-	+	-	-	-	+	HI or CI
15	-	-	-	-	+	-	-	-	+	HI or CI
16	-	-	-	-	+	-	-	-	+	HI or CI
17	+	-	-	-	+	-	-	-	-	CI or HI or RI or R
Controls										
1	-	-	+	-	+	-	-	-	-	HI or CI
2	-	-	+	-	+	-	-	-	-	HI or CI
3	-	-	-	-		+	-	-	+	AI or RI
4	+	-	-	+	+	-	-	-	-	CI or RI or R
5	-	-	+	-	-	-	-	-	-	HI or HV
6	-	+	+	-	-	-	-	-	-	CI
7	-	-	+	-	-	-	-	-	-	HI or HV
8	-	-	+	-	+	-	-	-	-	HI or CI
9	-	-	+	-	+	-	-	-	-	HI or CI
10	+	-	+	-		-	-	-	+	CI or RI or R
11	-	-	+	-	+	-	-	-	-	CI

NHL, Non Hodgkin lymphoma; C, control; (+), detected; (-), not detected; RI, re-infection; R, reactivation; CI, chronic Infection; AI, acute Infection; HI, history of Infection; HV, history of vaccination; NCfr, not confirmed.

(Arjmandi et al., 2011). HBV has the potential to replicate in extra hepatic tissues like lymphoid organs and especially invade B lymphocytes with unknown pathogenesis and may participate in malignant transformation of mononuclear cells and development of NHL (De Martel et al., 2009;

Mostafa et al., 2003; Wu et al., 2006; Kim et al., 2002; Marcucci et al., 2006; Chen et al., 2008; Lim et al., 2007).

Some researchers introduced an association between HBV infection and NHL (De Martel et al., 2009; Mostafa et al., 2003; Mehdi et al., 2006; Park et al ., 2008; Chen et al., 2008; Lim et al., 2007; Kuniyoshi et al., 2001; Wang et al., 2007). In earlier studies, chronic carriers of HBV have been shown to significantly increased risk between 2 and 5 fold for NHL (De Martel et al., 2009; Kim et al., 2002; Ulcickas Yood et al., 2007; Pioltelli et al., 2000). In Japan, HBV infection was diagnosed in NHL patients compared with controls, and also significant higher incidence of HBV infection was found among males (P= 0.05) (Kuniyoshi et al., 2001). Similarly, a significant higher prevalence of HBV infection was detected in patients with NHL compared with controls without malignancy (12.6% versus 4.7%, P= 0.001) (Kim et al., 2002). Also in another study, 7.3% of patients with NHL in comparing with 1.2% of healthy blood donors was significantly infected by HBV (P <0.005) (Takai et al., 2005). Similarly, in Italy, HBV was significantly diagnosed in 8.5% of patients with B-cell NHL compared with 2.8% of control group (Marcucci et al., 2006). In Romania HBV was found in 30.8% of NHL patients, which was significantly higher than the prevalence of 6.3% in the healthy controls (P <0.0001) (Cucuianu et al., 1999). Totally, these earlier reports suggest that HBV may play an inducing role in of pathogenesis of NHL. This phenomena was similarly found in this study by detection of significantly higher prevalence of HBV DNA in NHL patients compared with controls (11.6% versus 2%; P= 0.013). This significant difference was also found in the prevalence of HBcAb-IgG in NHL patients compared with controls (25.7% versus 8%; P= 0.013). Finding of the high prevalence of HBcAb-IgG in NHL patients suggests the immunity to previous infection and/or related to chronic infection of HBV.

In conclusion, an association between GBV-C/HGV and HBV and pathogenesis of NHL suggests that, rapid viral hepatitis replication or impaired host viral clearance may promote NHL pathogenesis. Therefore, careful efforts should be established in evaluation of the indicative role of GBV-C/HGV and HBV infections in larger groups of NHL patients and also recommend the introducing of preventive and controlling measures of these hepatitis viruses in NHL patients.

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Abbreviations

GBV-C, GB virus C; **EDTA,** ethylenediaminetetraacetic acid; **HGV,** hepatitis G virus; **HBV,** hepatitis type B viruses; **NHL,** non-Hodgkin's lymphoma; **HBsAg,** hepatitis B surface antigen; **HBeAg,** hepatitis B envelope antigen; **HBsAb,** hepatitis B surface antibody; **HBeAb**, hepatitis B envelop antibody; **HBc IgM Ab,** hepatitis B core IgM antibody; **PCR,** polymerase chain reaction; **RT-PCR,** reverse transcriptase-polymerase chain reaction; **ELISA,** enzyme-linked immunosorbent assay.

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