ORIGINAL ARTICLE

Hepatitis Monthly 2007; 7(2): 59-62

Analysis of the Related Factors in Hepatitis C Virus Infection Among Hemophilic Patients in Isfahan, Iran

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Background and Aims: **Patients with hemophilia are at high risk of post-transfusion hepatitis because of widespread use of plasma-derived products. As a consequence, hepatitis C virus (HCV) is the most common cause of chronic liver disease among hemophilic patients. The objectives of this study are to determine HCV prevalence, and analyze the effective agents in HCV infection in hemophilic patients.**

Methods: **All patients with inherited coagulation disorders registered in hemophilia center of Isfahan (553 persons) were checked for HBsAg and anti-HCV, using enzyme-linked immunosorbent assay (ELISA) test. Positive tests for anti-HCV were confirmed by RT-PCR. Clinical history, laboratory and treatment data of all cases were studied in January 2006.**

Results: **From 465 men and 88 women with inherited coagulation disorders with the mean age of 23.4 ± 12.9 years, 125 patients (22.6%) were HCV positive, 2 (0.4%) were HBV positive and one (0.2%) was both HCV and HBV positive. Odds ratio between HCV infection and cryoprecipitate usage was 3 (CI 95%: 2-4.5) and between HCV and factor usage was 0.21 (CI 95%: 0.07-0.7).**

Conclusions: **Considering the high chance of HCV infection after transfusion of cryoprecipitate and, a more careful pre-transfusion screening of blood for anti-HCV must be introduced in all blood banks. The usage of FFP less chance of HCV infection, instead of cryoprecipitate in patients who do not have volume restrictions may be preferable.**

Keywords: **Hepatitis C Virus, Hepatitis B Virus, Transfusion, Hemophilia, Iran**

Introduction

Hepatitis C virus (HCV) has emerged as a major cause of chronic liver disease worldwide [1, 2]. It is the most common cause of transfusion acquired non A- non B- (NANB) hepatitis [3]. More than 60% of individuals exposed to HCV develop chronic infection. Approximately 20 to 30% of the chronically infected individuals will develop liver cirrhosis and/or hepatocellular carcinoma when followed for 20 to 30 years [1].

Plasma products have revolutionized the care of hemophiliacs, reduced the degree of orthopedic deformity, and permitted virtually any form of surgery [4]. The widespread use of plasma products has also produced serious complications such as viral hepatitis, chronic liver disease and AIDS [4-6]. During the 1980 most hemophiliacs acquired HCV and many contracted HIV as well, becoming HCV/HIV co-infected [7, 8]. Consequently, methods have been developed to inactive the viruses, which became accessible in developed countries in the mid 1980s [9]. In the majority of developing countries, inactivated products were introduced

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Received: *17 Sep 2006* ***Revised:*** *18 Feb 2007*
Accepted: *18 Aug 2007*

Hep Mon 2007; 7 (2): 59-62

only in mid 1990, and the seroprevalence of HCV infection in hemophiliacs reported differently around the world [1, 3, 9, 10]. In Iran there were no HCV screening for plasma products which are distributed before 1997 [11], and there have been different reports about HBV and HCV infection among hemophiliacs [12, 13]. We performed this study to determine HCV, and its co-infection with HBV and HIV prevalence and related factors in central part of Iran.

Materials and Methods

From 1993 through 2006, hematologists and trained data managers collected demographic characteristics, clinical history, laboratory and treatment data and long-term complications in 553 patients with inherited coagulation disorders from medical records available at the Isfahan Hemophilia Society (IHS) and Hematology-Oncology Department, Isfahan University of Medical Sciences.

The IHS provides medical care to patients with hemophilia and allied disorders according to published guidelines [14-18]. The degree of hemophilia severity has been classified as mild, moderate and severe according to the plasma clotting factor activity (levels of 6-30%, 1-5% and <1%, respectively). Age, sex, state of residence, educational levels, frequency of each bleeding disorders and clinical characteristics (HIV, HCV and HBV status; first clinical presentation; most common bleeding symptoms) were all collected from the clinical records.

The laboratory assays used to measure the plasma levels of the deficient factors were standardized methods. All patients were checked for HBsAg, HIV and anti-HCV, using a standard enzyme-linked immunosorbent assay (ELISA) (Ortho® HCV 3.0 ELISA Test System; Ortho-Clinical Diagnostics, Raritan, NJ, USA). Positive tests for anti-HCV were confirmed by RT-PCR. All hemophilic patients underwent frequent testing for inhibitors and the development of an inhibitor was defined by a titer>0.5 Bethesda units (BU)/ml in any sample. Clinical history, laboratory and treatment data of all cases were studied in January 2006. The odds ratio of severity of hemophilia and blood product infusion and HCV infection calculated in SPSS 13.0 software. Quantities factor compare with chi-square test between hemophilic patients with and without HCV infection.

Results

465 male and 88 female with the mean age 23.4±12.9 were studied. Demographic data of hemophilic patients presented in Table 1. As shown in Table 2, the most common treatment type was cryoprecipitate. The most common complications were epistaxis (n=59), hemarthrosis (n=51) and hemophilic arthropathy (n=49). Replacement therapy primarily relied on cryoprecipitate and FFP. 27 patients showed factor inhibitor arising.

None of the patients were HIV positive but 125 patients (22.6%) were HCV positive, 2 (0.4%) were HBV positive and one (0.2%) was both HCV and HBV positive. In this study the odds ratio between HCV infection and cryoprecipitate usage was 3 (CI 95%: 2-4.5), between HCV and factor usage was 0.21 (CI 95%: 0.07-0.7), and between HCV infection and severe hemophilia were 2.9 (CI 95%: 1.9-4.2) (Table 3). In this study blood group, factor concentrate consumption, age and sex of patients have no predictive value in HCV infection. 44.4% of patients with factor inhibitor were HCV positive (P=0.006).

Table 1. Type and severity of hemophilia in studied patients

Parameter		N	Percent
Type of hematological disorder			
Hemophilia A		341	61.7
Hemophilia B		48	8.7
Von-willebrand disease		74	13.4
Platelet dysfunctions		34	6.1
Coagulation disorders	FV	30	5.4
	FVII	23	4.2
	Afibrinogenemia	13	2.4
	FX	10	1.8
	FVIII and FV*	19	3.4
Other disorders (FII & III)		3	0.6
Severity of hemophilia			
Mild		117	21.2
Moderate		101	18.3
Severe		228	41.2
Unknown		107	19.3

*Combination of these factors calculates separately in FVIII and FV disorders

Table 2. Treatment types of hemophilic patients

Parameters	N (%)	Sub-parameters	N (%)
Cryoprecipitate	298 (53.9)	Only Cryo	216 (39.1)
		With Factor	31 (5.6)
		With FFP or Transamin	51 (9.2)
Factor	97 (17.5)	Only Factor	53 (9.6)
		With FFP or Cryo	36 (6.5)
		With Transamin	8 (1.4)
FFP	88 (15.9)	Only FFP	60 (10.8)
		With Factor	5 (0.9)
		With Cryo or Transamin	23 (4.2)
Transamin	61 (11)	-	-
Platelet	17 (13.1)	-	-

Table 3. Odds ratio of blood products and severity of hemophilia in HCV positive patients

Parameter		HCV positive	HCV negative	Sig	OR	CI 95%
		N (%)	N (%)			
Cryo		76 (34.2)	146 (65.8)	0.000	3	2-4.5
FFP		15 (25)	45 (75)	0.6	1.1	0.6-2.2
Factor		3 (6.3)	45 (93.7)	0.003	0.21	0.07-0.7
Platelet		1 (11.1)	8 (88.9)	0.4	0.4	0.05-3.4
Transamin		1 (6.3)	15 (93.7)	0.1	0.22	0.03-1.7
Severity	Mild	9 (7.7)	108 (92.3)	0.000	0.23	0.11-0.47
	Moderate	27 (26.7)	74 (73.3)	0.26	1.3	0.8-2.1
	Severe	76 (33.3)	152 (66.7)	0.000	2.9	1.9-4.2

Discussion

There are different reports of HCV infection among hemophiliacs in several studies. The prevalence of HCV infection in southern part of Iran (15%) [12], Jamaica (41%), Brazil (32.6%) and (44.6%) are somehow near to our recent results [1, 3, 9]. Although there were some different methods employed to detect antibody and to confirm positive tests for anti-HCV. The higher prevalence in Japan (88.2%) as has been hypothesized may be due to use of unheated products [19]. The rates of HCV, HBV and HIV positivity in patients were considerably lower than those observed in other studies, and also in developing countries. In central part of Iran all patients escaped HIV infection, probably because of the early exclusive use of domestic products and the overall scarcity of HIV infection.

Transfusion-transmitted diseases are one of the most important complications and common causes of death seen in hemophilic patients [12, 13]; therefore, preventing these diseases is a major responsibility of the hemophilia center of Isfahan. The WFH divided the participating countries, in its global survey [12, 20], into three categories based upon annual gross national product (GNP): >US$ 10000; US$ 2000-10000; and <US$ 2000. According to the WFH data, as the GNP increases, life expectancy of hemophiliacs increases. For example, the comparison of the ratio of the number of adults to the number of children with hemophilia in countries with low GNP (annual GNP < US$ 2000) to the same ratio in high GNP countries (annual GNP > US$ 10000) suggests that hemophilia patients in the poorest countries normally do not survive past childhood [12, 20]. The mean age of our hemophilic patients was 23.4±12.9 years. Further increase in the mean age of our patients will be regarded as a sign of the improvement in hemophilia care program.

In this study blood group, factor concentrate consumption, age and sex of patients have no predictive value in HCV infection and it is similar to other studies performed before in Iran and other countries [13, 21]. Considering the high chance of HCV infection after transfusion of cryoprecipitate a more careful pre-transfusion screening of blood for anti-HCV must be introduced in all blood banks. The usage of FFP which has less chance of HCV infection, instead of cryoprecipitate in patients who do not have volume restrictions may be preferable. A more stringent policy for blood product usage, universal HCV screening and HBV vaccination is needed to abolish these diseases in patients with hemophilia.

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