brief report

Serum viral markers in Iranian patients with congenital bleeding disorder

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In the history of hemophilia treatment, the 1940s were a time of transition from primitive, conventional attempts to control bleeding episodes to transfusion therapy, which represented a major accomplishment.[1,2] Even though the discovery of cryoprecipitate and factor concentrates and lyophilized concentrates led to great improvements in both longevity and quality of life for persons with hemophilia, at the same time a group of tragic setbacks were reported.[2,3] These important negative consequences were complications resulting from transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). It was discovered that virtually all hemophilia patients exposed to non-heat-treated factor were HCV positive, and over 50% of hemophilia patients in the United States had HIV seroconversion, and 5% to 10% of such patients became chronic carriers of hepatitis B.[3-7]

The Iranian Hemophilia Center was established as a main health care system for the Iranian hemophilia population in 1965.[8] This reference center provides easy access for hemophilia patients and their families for early diagnosis and treatment. The programs for control of HBV and HCV infection in Iran were started in 1993 with routine HBV vaccination followed by screening for HCV in blood products in 1997.[1,4] In this study, we determined the prevalence of viral infections, specifically HCV, HBV, and HIV, the impact of HIV on HCV infection, and the genotypes of HCV (in view of the risk of viral transmission throughout blood injection and the outbreak of HIV and HCV in blood donors) in Iranian hemophiliacs.

PATIENTS AND METHODS

In a cross-sectional and prospective study, we enrolled all hemophiliac patients attending the Iranian Hemophilia Center during the year 2003, to determine their virological, clinical and epidemiological characteristics for chronic viral infections. A complete virological, biochemical and epidemiological assessment was done for all hemophiliacs registered at the center. They were tested for anti- HCV-ELISA-3, hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (HbsAb), hepatitis B core antibody (HbcAb) and HIV serology. The patients with positive anti-HCV were tested for HCV-RNA to obtain serological confirmation. Genotype was also determined. Clinical information collected included age, gender, type of hemophilia (A or B or other) and blood products transfused to patients, severity of hemophilia (classified as severe if factor VIII or IX blood levels were less than 1%, moderate if they were between 1 and 5% and mild if they were greater than 5%). Data were analyzed with the chi-square test, using SPSS v.11.5 software.

RESULTS

Of 236 patients included, 73% had hemophilia A, 10% hemophilia B, and 17% had other types of congenital coagulopathies like platelet disorder and factor V deficiency. Most of the patients were in the third decade of life. The mean and standard deviation for age was 26.6±12.1 years (Table 1). More than 80% of patients were anti-HCV (ELISA) positive. Forty four percent of patients with positive HBcAb, which indicated contact with hepatitis B virus. In this population only 3% of patients were chronic carriers for hepatitis B virus. About 80% of patients had HBsAb in their blood and showed natural or vaccine immunity to HBV. Only less than 5% of patients were HIV seropositive (Figure 1).

No child under the age of 10 years was anti-hepatitis C virus, HBsAg, or anti-HIV (ELISA) positive; in contrast the frequency of these infections among older subjects were higher. The age distribution of positive anti-hepatitis C virus and HBcAb differed significantly among the hemophiliacs ($P<.05$). The anti-HCV (ELISA) positivity significantly increased in hemo-

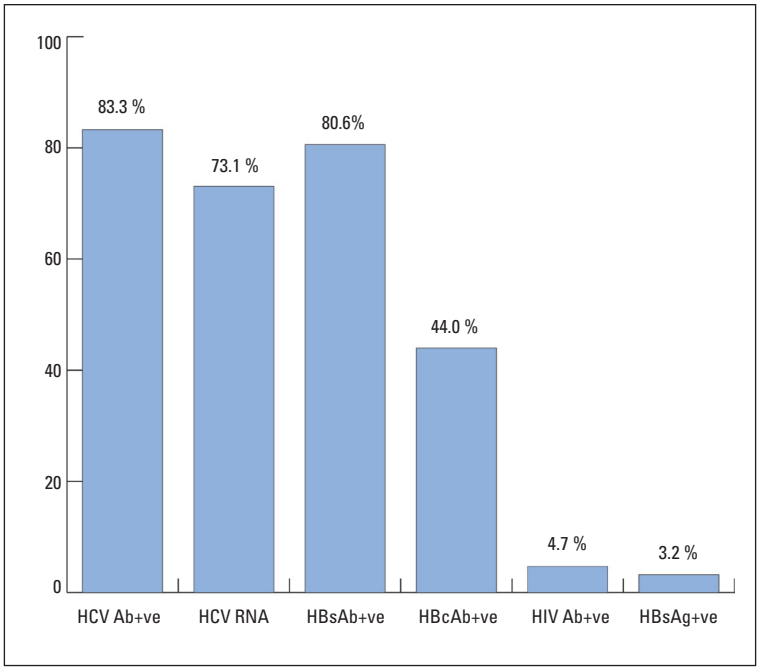

Figure 1. Frequency of viral markers in Iranian hemophilia patients (n=236).

Table 1. Demographic and clinical characteristics of 236 patients with hemophilia.

	Hemophilia A	Hemophilia B	Others*	Total
Gender				
Female	2	1	18	21 (8.9%)
Male	169	24	22	215 (91.1%)
Age				
Range (y)	4.0-60	6.0-69	9.0-58	4.0-69
Mean±SD	26.1±11.1	32.5±15.9	25.5±12.5	26.6±12.1
0-9 y	2	2	1	5
10-19 y	47	2	16	65
20-29 y	70	9	13	92
30-39 y	29	6	4	39
40-49 y	15	2	2	19
50-59 y	7	1	4	12
>60 y	1	3	0	4
Severity				
Severe	128 (74.9%)	16 (64.0%)	-	144 (73.5%)
Moderate	24 (14.0%)	3 (12.0%)	-	27 (13.8%)
Mild	19 (11.1%)	6 (24.0%)	-	25 (12.8%)
Total	**171 (72.5%)**	**25 (10.6%)**	**40 (16.9%)**	**236 (100%)**

Data are number of patients (percentage unless specified otherwise. *Others= platelet disorders, factor V deficiency.

philia A and B compared to other congenital coagulopathies (platelet disorders and factor V deficiency) ($P<.05$). There was a marked difference in anti- HCV (ELISA) positivity among patients classified by severity of coagulopathies in hemophilia A and B ($P<.05$). Eight HIV-positive patients were exposed to the HCVAb test and they were all diagnosed positive, but no concrete result could be achieved due to the low number of samples (taken from only eight patients). There were fewer anti-HCV (ELISA) positive tests in hemophilia patients with HBsAg positivity. The anti-HCV test (ELISA) was positive in 2 of 5 HBsAg positive hemophilia patients in contrast to 134 of 160 HBsAg negative hemophilics ($P=.03$). The hepatitis C virus RNA test by reverse transcriptase-polymerase chain reaction (RT-PCR) was positive in 80.2% of anti-hepatitis C virus (ELISA) positive hemophilia patients. In PCR-positive patients, genotyping was performed; genotype 1a (48.5%) was the predominant type and genotype 3a (33.3%) was common. Four patients were infected with type 1b (12.1%), one patient with type 2b (3%), and one patient with type 4b (3%).

DISCUSSION

Before 1997, hemophiliacs in this center were treated with imported lyophilized concentrates and locally produced cryoprecipitate and fresh frozen plasma without viral inactivation treatment. This could have led to early exposure of this population to contaminated clotting factor products. The high prevalence of HCV infection observed in this hemophiliac population (80%) indicates that hepatitis C is a major contributor to the morbidity of persons with hemophilia in Iran. This high prevalence is comparable to the prevalence in developed countries[9,10] where patients have good access to products and where there was widespread use of clotting factor concentrates as replacement therapy before the era of inactivated products.

As in the general hemophiliac population, hemophilia A was the predominant type (73%). The risk of infection with each of these viruses is related directly to the severity of the hemophilia. The predominance of severe hemophilia was expected in a population infected by HCV with such a high exposure. Individuals with more severe disease require more clotting factor, thus increasing their risk of bloodborne infections. This shows that the likelihood of infection increases with bleeding frequency and amount of factor used.

Another important problem is co-infections, especially hepatitis C and HIV. As expected, given their similar routes of transmission, such coinfection is common among persons with hemophilia.[11,12] We found a lower

prevalence of HIV infection in our hemophilia population compared to developed countries.[13,14] Based on anecdotal observations in our center, the lower survival of HIV positive patients could lead to a lower number in our registry. However, co-infection, especially with HIV, has been growing in importance because these patients are at a higher risk of progression to chronic liver disease than those infected with HCV alone.[2,14,15] This is illustrated by our data, which indicated that among HIV-infected subjects, 100% were HCV positive and these patients had a lower serum albumin level and a higher ratio of prolonged prothrombin time.

Children who were born after 1993 had no evidence of HCV, HBV, and HIV infection. Others have observed this low risk as well.[16-18] Although the incidence of new infections with HBV, HCV, and HIV has decreased substantially in recent years, chronic liver disease by these viruses continues to be of significant concern to persons with hemophilia.

The distribution of HCV genotypes in the studied population did not significantly differ from the published data on the hemophiliac and non-hemophiliac populations in Iran, where genotype 1a infection is predominant.[17,18] Actually, the distribution of HCV genotype is similar to that in England, European countries and the USA, where the distribution usually reflects the origin of the blood donors used in the manufacture of imported pooled factor VIII and IX concentrates.[18] In Iran, the HCV genotype distribution would be more a reflection of indigenous and some intermixing of strains with strains from other parts of the world.

In conclusion, this study provides evidence that HCV infection is a major problem for Iranian hemophiliacs. HCV infection is more prevalent in older patients, in those with more severe coagulopathies and in HIV co-infection.

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