

BRIEF
REPORTSerological Markers of Blood Borne Viruses among
Persons with Combined Factor V & VIII DeficiencyHassan Mansouritorghabeh ^{1*}, Reza Farid Hosseini ¹, Aliakbar Pourfathollah ², Azizollah Behjati ¹¹ Immunology Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran² Experimental Hematology and Blood Banking Group, Medical Sciences School, Tarbiat Modarres University (TMU), Tehran, Iran

Background and Aims: Combined factor V and VIII deficiency (CF5F8D) is a rare hemorrhagic disorder. Treatment of patients with blood products has been associated with infections with blood-borne viruses. Due to absence of any survey on status of blood borne viruses in individuals with CF5F8D, we tried to address this question.

Methods: Among 25 known cases, 24 individuals were assessed for hepatitis B and C viruses (HBV & HCV), human T lymphotropic virus type one (HTLV-I) and human immunodeficiency virus type1/2 (HIV1/2) using enzyme linked immunosorbent assay method.

Results: In the group under survey, 2 cases (8.3%) were positive for anti-HCV. There was no infection with HBV, HTLV-I and HIV.

Conclusions: Hepatitis C is a major health problem in CF5F8D, as in hemophiliacs, and may need more attention from manufacturers of blood products and more careful pre-transfusion screening of blood products for anti-HCV.

Keywords: CF5F8D, Hemophilia, HCV, HBV, HIV1/2, HTLV-I

For the first time, combined factor V and VIII deficiency (CF5F8D) was reported by Oeri *et al.* ⁽¹⁾. Affected individuals have between 5 to 30% of normal plasma levels of factor V and factor VIII antigen and activity. Inherited CF5F8D is a rare occurrence: a total of 106 recognized cases were reported according to a literature review in 1998 ⁽²⁾ and according to our current review of literatures, the total number of affected individuals until the end of May 2007 is about 150 persons ⁽³⁾. Most patients are from Mediterranean region including Iran, where due to high rate of consanguine marriage, about 77 cases with CF5F8D were reported until the end of 2007 ⁽⁴⁾.

Treatment of patients with blood products has been associated with infections with blood-borne viruses. Of these, hepatitis B and C viruses (HBV & HCV, respectively) and the Human Immunodeficiency Virus (HIV) have created major health problems. The haemostatic level can be achieved by plasma infusion and factor VIII concentrate as a source of factor V and factor VIII, respectively. There are reports of successful managements of major surgery, circumcision, dental extraction and prostatectomy

in these individuals with infusion of fresh plasma and plasma exchange ⁽⁵⁾. In this report, we tried to address blood borne viruses profile (HTLV-I, that is endemic in north-eastern of Iran, HIV, HBV and HCV) in the second largest group of individuals with CF5F8D in the world.

Twenty-four persons (8 females (33.3%) and 16 males (66.6%) with a mean age of 26.95 ± 15.12 years ranging from 6 to 61) with CF5F8D from northeastern Iran were invited to Ghaem Hospital during March and April 2007 for filling out a questionnaire and blood sampling. All of them have

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received coagulation factor VIII concentrate and plasma on demand. They were evaluated for the presence of serum hepatitis C virus antibody (HCV-Ab), hepatitis B surface antigen (HBsAg), human immunodeficiency virus type 1 and 2 (HIV1/2), and human T lymphotropic virus type one (HTLV-I) and liver function tests.

The presence of IgG antibody to HCV, HTLV-I/II and HIV1/2 and HBsAg were tested with third-generation enzyme-linked immunosorbent assay (ELISA) based test kits according to manufacturers' instructions (HBsAg kit by Bio Merieux, Boxtel, Netherlands & HTLV-I, HIV1/2 and HCV kits by Dia Pro, Milano, Italy). The positive cases for anti-HCV were demonstrated by reverse transcriptase-polymerase chain reaction (RT-PCR) method in genetic laboratory of hemophilia center in Tehran. The level of alkaline phosphatase (ALP), aspartate

aminotransferase (AST) and alanine aminotransferase (ALT) were measured using enzymatic colorimetric methods. ALP levels higher than 140 U/L for adults and 370 U/L for children were regarded as upper limit. The levels of ALT higher than 41 U/L for males and greater 31 U/L for females were regarded as out of reference interval. Also upper limits of AST for males and females were 37 and 31 U/L, respectively.

Among 16 males and 8 females (mean age = 27.7 ± 15.24), the youngest was a 6-year-old boy and the oldest was a 61-year-old male (Table 1). The minimum and maximum percent of factor V was 4 and 15 with a mean of 9.27 ± 3.22 percent. The minimum and maximum percent of factor VIII was 3.20 and 30 with a mean of 13.23 ± 6.8 percent, respectively. Regarding liver function tests, the minimum and maximum level of ALT was 11 and

Table 1. Hematological, biochemical and viral serology of 24 individuals with combined factor V and VIII deficiency

No.	Family	Age (yr)	Sex	Factor VIII (%)	Factor V (%)	ALT (U/L)	AST (U/L)	ALP (U/L)	HTLV-I	HBsAg	HIV	HCV
1	1	17	M	3.2	14	14	17	220	-	-	-	-
2	1	6	M	7	6	12	7	53	-	-	-	-
3	1	25	M	9	6	49	37	61	-	-	-	+
4	1	16	F	9	9	19	15	61	-	-	-	-
5	1	10	M	3.9	9	20	23	60	-	-	-	-
6	2	23	F	19.5	15	16	19	72	-	-	-	-
7	3	32	M	10	4	19	21	74	-	-	-	-
8	4	48	M	30	6.5	26	27	80	-	-	-	-
9	5	42	F	16	13	11	9	47	-	-	-	-
10	5	39	M	13	12	30	29	50	-	-	-	-
11	5	42	M	22	5	17	23	50	-	-	-	-
12	5	61	M	15	9	27	17	72	-	-	-	+
13	6	48	F	15	15	30	23	60	-	-	-	-
14	6	45	M	12	10	28	17	220	-	-	-	-
15	6	47	M	10	10	12	15	117	-	-	-	-
16	6	8	M	8	4	22	18	108	-	-	-	-
17	6	23	F	8	9	49	55	118	-	-	-	-
18	6	24	F	5	9	27	31	94	-	-	-	-
19	6	18	M	6	9	17	20	134	-	-	-	-
20	7	22	F	20	9	21	23	41	-	-	-	-
21	7	24	M	19	10	24	27	52	-	-	-	-
22	7	12	M	20	10	21	23	115	-	-	-	-
23	8	22	M	21	13	23	29	46	-	-	-	-
24	8	11	F	16	6	20	33	130	-	-	-	-

U/L: unit per liter; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; HTLV-1: human T-lymphotropic virus type 1; HIV: human immunodeficiency virus; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus.

49 with a mean of 23.08 ± 9.69 U/L while AST, with a mean of 23.41 ± 9.76 U/L, ranged from a minimum of 7 to a maximum of 55 U/L. Minimum and maximum ALP level was 41 and 220 respectively with a mean of 83.83 ± 41.03 U/L. There were no cases with HTLV-I, HBV and HIV 1/2 infections in this group, but there were 2 cases (No. 3 & 12 in Table 2) with HCV infection (8.3%). Two cases had AST and ALT levels higher than normal (cases 3 and 17). The cases number 1 and 14 had ALP higher than normal (220 U/L).

Although plasma products have revolutionized the care of individuals with hemorrhagic tendencies, widespread use of plasma products has also produced serious complications including viral hepatitis, chronic liver disease and acquired immunodeficiency syndrome (AIDS). There are many reports about HCV and HBV infections in hemophiliacs in Iran (6-11) stating that the overall prevalence of HCV-Ab and HBsAg seropositivity in hemophiliacs in various part of Iran is 41.12% and 8.25%, respectively (Table 2). These findings showed that HBV infection is more noticeable in hemophiliacs at Guilan (North of Iran) and Tehran (Capital of Iran). HCV infection is a major problem in individuals with hemophilia in Iran; on the other hand, we currently do not know a perfect vaccine against it. There are a few reports on the existence of HIV positive cases in hemophilic population. Also it seems that HTLV-I and HTLV-II have the least frequency in individuals with hemorrhagic tendencies. A reason for this may be the fact that HTLV-I/II is transmitted through cellular products, while individuals with bleeding disorders usually use plasma products that are largely depleted of white blood cells.

However, most CF5F8D individuals in this study had mild to moderate bleeding manifestations, so they have been less exposed to coagulation products. It seems that this group has used less blood products and so has been less exposed to blood-borne viruses. In this group, the most common viral infection was hepatitis C (8.3%), and there were no infected persons with HBV, HIV1/2 and HTLV-I. The case number 3 (positive for HCV antibody) and case number 17 (negative for HCV antibody) both had high levels of AST and ALT and were referred to a hepatologist for further evaluations. Cases number 1 and 14 were asked to be visited 2 months later for rechecking liver function tests. It seems that the current program of Iranian Blood Organization for

Table 2. The prevalence of HBsAg, anti-HCV and anti-HIV in hemophiliacs in some provinces of Iran.

Province	HBsAg (%)	Anti-HCV (%)	Anti-HIV (%)	Reference
Guilan	26/92 (28.2)	70/92 (76)	NR	(6)
Fars	2/282 (0.7)	44/282 (15.6)	1/282 (0.3)	(7)
Yazd	1/74 (1.4)	36/74 (48.6)	1/74 (1.4)	(8)
Kerman	1/97 (1.0)	43/97 (44.3)	NR	(9)
East Azarbayjan	3/130 (2.3)	72/130 (55.3)	1/130 (0.7)	(10)
Tehran	41/53 (23.3)	106/176 (60.2)	4/176 (2.3)	(11)
Khorasan	1/180 (0.5)	53/180 (29.4)	0/180 (0)	Unpublished data
Total	75/908 (8.2)	424/1031 (41.1)	7/842 (0.8)	-

NR: not recorded; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus.

using permanent donors and encouraging only healthy volunteers for blood donation may be a reasonable option for improving the safety of blood products. It is recommended to individuals with CF5F8D to have both liver function tests and anti-HCV tested at least every 6 months.

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