Original Article

The Risk Factors of Inhibitor Development and Hepatitis C Virus among Hemophilic Patients in Children Welfare Teaching hospital

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Summary:

Background: Inhibitor development and HCV are considered the most serious complications of hemophilia treatment. Many factors may increase the risk of complications which include: type of hemophilia, age of the patient, age of onset, duration of the disease, & number of replacement per month.

Patients and methods: A descriptive study included 200 patients less than 20 years of age admitted to the Hemophilia Center in Children Welfare Teaching Hospital , medical city in Baghdad , their data (ag , sex , disease onset and duration , severity of hemophilia) were collected over 8 months period from 1st January to 31st August 2006. Mixing tests and serology tests for HCV and HBV were performed for all patients.

Results: The study showed that 156 (78%) patients had hemophilia A, 44(22%) patients had hemophilia B, and 122 (61%) patients were older than 10 years, in 166 (83%) patients the disease was diagnosed before 2 years of age. Twenty (12.8 %) patients with hemophilia A and 4(9%) patients with hemophilia B developed inhibitors (+ve mixing test). Age more than 10 years, disease onset before 2 years and severe hemophilia were the most common associated findings in patients with inhibitors in 19(79%) , 22(91%), 15(62.5%) patients respectively. Eighty (40%) patients had HCV and 6(3%) patients had HBV, patients older than 10 years , disease duration more than 5 years and severe hemophilia were the most common associated findings with HCV in 68(57.6%), 64 (56%), and 44(45%) patients respectively.

Conclusions: The risk of inhibitor development was associated more with Hemophilia A, age more than 10 years, early onset and severe disease but the association was statistically insignificant. The rate of HCV infection was high, that needs special attention and effective screening program.

Keywords: Hemophilia**,** Inhibitors, and Hepatitis**.**

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Introduction:

Hemophilia (A and B) due to factor VIII and X1 deficiency are the most common bleeding disorder. Factor VIII and IX participate in the activation of factor X together with phospholipids and calcium, essential for activation of prothrombin to thrombin which converts fibrinogen to fibrin clot that prevent hemorrhage (1,2,3) .

Lab. Findings include prolonged APTT, with normal other screening haemostatic tests (platelet count, bleeding time, PT and TT). Factor assay should be done to confirm the diagnosis and to assess severity of disease in which factor level in severe hemophilia is less than 1.0 U/dl , moderate hemophilia have 1–5 U/dl , mild hemophilia have levels greater than 5 U/dl (2) .

Mixing study is done if there is an unexplained prolongation of the PT, PTT, or thrombin time. Correction of the PT or PTT by 1:1 mixing with normal plasma suggests the deficiencies of a clotting factor. If the clotting time is not corrected, only partially corrected, or becomes more prolonged and the patient has clinical bleeding, an inhibitor (antibody directed against) of a specific clotting factor, most Commonly factor VIII, or IX or XI, may be present (2) Inhibitors are antibodies directed against factor VIII and IX. Failures of bleeding episodes to respond to appropriate replacement therapy are the usual 1st sign of the inhibitor (4).Inhibitors develop in approximately less than 15% of patients with hemophilia A and less than 3% of patient with hemophilia B (5,6) .

Risk factors for inhibitors development are related to early age of onset, severity, type of treatment and genetics. (7, 8, 9)

Risk of acquiring blood born disease, e.g. hepatitis B, C is considered as the major cause of morbidity and mortality among hemophilia patients receiving contaminated blood products or factor concentrate which did not have adequate viral inactivation step in the purification process (10, 11). Prevalence of HCV in hemophilia patients is 27.2% and HBV is 3 %. Mortality of hepatitis among hemophilia patient is 16.7 times greater than general population (11, 12).

Patients and methods:

A cross sectional study was carried out in the hemophilia center in Children Welfare Teaching Hospital, Medical city in Baghdad. The records of 200 patients with hemophilia were analyzed, & the following data were collected: age, sex, residence,

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family history, past medical history, type of hemophilia , age of onset, and severity of the disease , frequency of factor and blood products transfusion per month and result of the serological viral markers (HBsAg , anti –HCV Ab , HIV).

Mixing studies were done for all the patients in hemophilia lab of Children Welfare Teaching Hospital The correction of the PTT would confirm the diagnosis of hemophilia. If the correction does not occur on mixing, an inhibitor may be present. The results were analyzed using the Chi- Square test. P-Value <0.05 is consider to indicate significant association.

Results:

The total number of patients was 200. Out of them 156 (78%) had hemophilia A, 44 (22%) patients had hemophilia B. The mixing test was positive in 20(12.8%) of hemophilia A patients and 4(9%) of hemophilia B patients as shown in table –1.

Regarding the relation of inhibitor development and the age of hemophilic patients: it was found that 19% of hemophilic patients were under 5 years old in which 5.2% of them had (+ve) mixing test, 20% were between 5-10 years old and 7.5% of them had (+ve) mixing test, 27% of patients were between 10-15 years old in which 9.2% of them had (+ve) mixing test and 34% of hemophilic patients were between 15-20 years old and 20.5% of them had (+ve) mixing test. P-value >0.05 (not significant) as shown in table –2.

Regarding the relation of inhibitor development and the age of onset of hemophilia, the study found that inhibitors had developed in 13.1% of hemophilic patients who were diagnosed before I year of age, 13.6% of patients diagnosed between 1-2 years old, and 5.8% of patients diagnosed after 2 years. P-value >0.05 as shown in table –3

The development of inhibitors was found in 16.6% of patients with severe hemophilia, 11.7% in moderate hemophilia, and 5% in mild hemophilia. P->0.05 as shown in table – 4.

Hepatitis C was found in 40% of cases , 3% had hepatitis B as shown in table – 5 , also 47.5% of hemophilia A & 13.6% of hemophilia B were infected with hepatitis C virus as shown in table – 6 .

It was shown that 11.1% of hemophilic patients with hepatitis C were less than 5 years old, while 17.3% of patients were between 5-10 years old, 48% of patients were between 10-15 years old, and 65% of patients between 15-20 years old. P-value was <0.001 (highly significant), as shown in table – 7,

In 56% of patients with disease duration more than 5 years hepatitis were positive in comparison with 18.6% of patients with the disease duration less than 5 years. P-value was<0.001(highly significant), as shown in table – 8.

In 34.7% of mild hemophilic patients, 34.4% of moderate hemophilic patients , and 45% of severe hemophilic patients were infected with hepatitis C virus. P- Value was >0.05 (not significant) , as shown in table – 9 .

The study showed that 27.5% of patients who required factor replacement <4 times /month, 14.2% of patients who required factor replacement between 4-8 times/ month, and 48.8% of patients who required factor replacement >8 times per month were infected with hepatitis C virus. P-value was <0.05 (significant), as shown in table – 10.

Table no.1: Relation between inhibitor development and type of hemophilia.

type	Mixing test (+ve) (Inhibitor)	Mixing test (- ve) (Non inhibitor)	Total no. (%)
	No. (%)	No. (%)	
Hemophilia A	20 (12.8%)	136 (87.2 %)	156 (78%)
Hemophilia B	4 (9%)	40 (91 %)	44 (22%)

Table no. 2: Relation between inhibitor development and Age of hemophilia patients.

Age (year)	Mixing test(+ve) (Inhibitor)		Mixingtest (-ve) (Non inhibitor)		Total no. (%)
	No.	%	No.	%	
0 -5	2	5.2	36	94.8	38 (19%)
>5-10	3	7.5	37	92.5	40 (20%)
>10-15	5	9.2	49	90.8	54 (27%)
>15-20	14	20.5	54	79.5	68 (34%)

P-value>0.05

Table no.3: Relation between inhibitor development and age of onset of hemophilia:

Age (year)	Mixing test (+ve) (Inhibitor)		Mixing test (-ve) (No inhibitor)		Total no. (%)
	No.	%	No.	%	
0-1	16	13.1	106	86.9	122(61%)
1-2	6	13.6	38	86.4	44(22%)
>2	2	5.8	32	92.4	34(17%)

P-value >0.05

Table no. 4: Relation between inhibitor and Severity of hemophilia:

Severity	Mixing test (+ve) (Inhibitor)		Mixing test (-ve) (No inhibitor)		Total no. (%)
	No.	%	No.	%	
Severe	15	16.6	76	38.4	91 (45.5%)
Moderate	6	11.7	45	88.3	51 (25.5%)
Mild	3	5.1	55	94.9	58 (29%)

P-value>0.05

Table no. 5: No. of patients with hepatitis B, C:

Serological test	No.	%
HCV	80	40%
HBV	6	3%
(-v) serological test	114	57%
Total	200	100%

Table no.6: Relation between hepatitis C virus and type of hemophilia:

Type of hemophilia	HepatitisC (+ve)		Hepatitis C (-ve)		Total no. (%)
	No.	%	No.	%	
Hemophilia A	74	47.5	82	52.5	156(71%)
Hemophilia B	6	13.6	38	68.4	44(22%)

Table no.7: Relation between age of patients and hepatitis C virus:

Age	Hepatitis C (+ve)		Hepatitis C (-ve)		Total no. (%)
	No.	%	No.	%	
0 -5	4	(11.1%)	32	(88.9)	36(18%)
>5-10	8	(17.3%)	38	(82.7)	46(23%)
>10-15	26	(48%)	28	(52)	54(27%)
>15-20	42	(65%)	22	(35)	64(32%)

P-value <0.001 (highly significant)

Table no.8*:* Relation between hepatitis C virus and the duration of the disease as follow:

Duration	Hepatitis C (+ve)		Hepatitis C (-ve)		Total no. (%)
	No.	%	No.	%	
Birth -5 years	16	18.6	70	81.4	86(43%)
>5 years	64	56	50	44	114(57%)

P-value <0.001 (highly significant)

Table no. 9: Relation between hepatitis C virus and severity of hemophilia:

Severity	Hepatitis C (+ve)		Hepatitis C (-ve)		Total no. (%)
	No	%	no	%	
Mild	16	34.7	30	65.3	46(23%)
moderate	20	34.4	38	65.6	58(29%)
Severe	44	45	52	55	96(48%)

P- Value >0.05

Table no.10: Relation between hepatitis C virus and frequency of blood product replacement therapy per month:

No. of replacement/ month	HepatitisC (+ve)		Hepatitis C (-ve)		Total no. (%)
	No.	%	No.	%	
<4	16	27.5	42	72.5	58(29%)
4-8	20	14.2	32	85.8	52(26%)
>8	44	48.8	46	15.2	90(45%)

P-value <0.05(significant)

Discussion:

Inhibitors development against FVIII and FIX is one of the most important complications in hemophilia patients. Many factors may play important role in inhibitor development, these factors include: type of hemophilia, age of the patients, severity and duration of the disease. The study showed that 11.2% of hemophilia A patients develop inhibitors and 9% of hemophilia B patients had developed inhibitors and these findings are consistent with study done by Mahasandana (13) in which inhibitors development was found to be 10% in patients with hemophilia A , while it was different regarding hemophilia B patients where only 3% scored in Mahasandana study , which may be caused by different replacement therapy other than the factor replacement which is considered as a risk factor for inhibitor development. In Egypt, a study done by Abdul Razik found that prevalence of inhibitor in hemophilia A patients was 15% & 5% in hemophilia B patients (6). It was found that the

development of inhibitors was higher among patients older than 10 years 15.5%, than those younger than 10 years of age 6% .This is consistent with a study done by sultan in France in which 18% of patients older than 10 years old had developed inhibitors (5). The development of inhibitors was the highest 13.5% in patients who were exposed to FVIII & XI for the first time before 2years of age, compared to 5.8% of patients with 1st exposure to factor replacement after 2 years of age, this goes with a study done by Chalmers in U.K (7) which found a rate of 20% in hemophilic patients diagnosed below 2 years of age and 8% in those diagnosed older than 2 years, this is also goes with a study done by Gouw in Netherland (8) . Old patients and those who are frequently exposed to factor and blood products early in life are prone to more risk of antibody development (7, 8, and 9). Inhibitors development was more among severe hemophilic patients, 16.6% in response to multiple infusion of factor VIII & XI concentration compared to 11.7% of moderate hemophilia and 5% of mild hemophilia patients, and this is consistent with the study done by Kagehiro in Japan in which 20% of severe hemophilia patients developed antibodies (14) . and study done by Ehrenforth in Germany in which 16% of severe hemophilia patients developed inhibitors (15) . The risk of hepatitis B and C among hemophilia patients is related to many factors that play an important role especially in hepatitis C infection. These factors include type of hemophilia, age, duration of the hemophilia, severity of hemophilia and frequency of blood products replacement per month.The study showed that 40% of hemophilia patients had HCV and 3% of patients had HBV. The seropositivity of hepatitis B and C virus was found to be 26% for HCV and 1% for HBV in a study done by Zaid in Jordan (16) and 22% of HCV and 1% of HBV in a study done by Lilia Lopes in Uruguay (17) . Also the study found that 50% of hemophilia A patients, 13.6% of hemophilia B patients had hepatitis C virus, this is consistent with a study done in Egypt in which 44% of hemophilia A patients and 10% of hemophilia B patients had hepatitis C virus (6) . Hepatitis C was high among older age group, 14.6% of patients less than 10 years of age were infected with hepatitis C, compared to 57.6% of patients older than 10 years, this is consistent with Jordanian study done by Zaid-H (16) . The duration of hemophilia was an additional risk factor for developing hepatitis C, 56% of patients more than 5 years duration of hemophilia had hepatitis C virus, in comparison with 18.6% of hemophilia patients with the disease duration less than 5 years. This goes with a study done by Jean- Pierre Allian in France (18). The severity of hemophilia had some relation to hepatitis C virus infection, thereby it was found that 45% of severe hemophilic patients had hepatitis C virus, compared to 34.4% of patients with moderate hemophilia, and 34.6% of mild hemophilia patients, this is because severe hemophilic patients require more blood products replacement with a higher risk of hepatitis C virus infection . This is consistent with the study done by Schinp in England (16), which found that 41% of hemophilia patients were infected with HCV. There is a significant relation between the frequency of blood products replacement per month and hepatitis C virus infection , 48.8% of hemophilic patients who had received blood products >8 times per month had hepatitis C virus compared to 27.5% of those received blood products <4 times per month, this goes with the study done by Jean –Pierre (18).

Conclusions:

The development of antibodies against FVIII and FIX was associated with the type of hemophilia, age of patient, duration of the disease and severity of hemophilia although it did not achieve statistically significant association .The rate of Hepatitis C was significantly high, that needs special attention and frequent screening especially in chronic receivers of blood products. The seropositivity of HCV infection is strongly associated to age, number of blood products transfusion per month, duration of the disease, and severity

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