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The Epidemiological Characteristics of Hepatitis C Virus Among Patients with Inherited Bleeding Disorders

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Abstract
Background: Patients who frequently receive blood and or blood products have high risk of hepatitis C virus (HCV) infection.**Objectives:** To evaluate the prevalence of (HCV) infection and determine potential risk factors among patients with inherited bleeding disorders.**Patients and Methods:** Across sectional retrospective study was conducted in the Hemophilia unit in Children Welfare Teaching Hospital, Medical city in Baghdad; between 1st of Juneof2014 to 1stof January of 2015. The medical records of 1158 patients with hemophilia A& B, von Willebrand disease (vWD), thrombosthenia, factors VII, X, XIII deficiencies and hypofibrinogenemia; of all ages were analyzed for the presence of HCV antibody using (ELISA) and for HBs antigen as co-infection.**Results:** The overall prevalence of HCV infection was (13.2%). Of total, 595 (51.4%) patients had hemophilia A and 99 (16.6%) were anti-HCV positive, while 225 (19.4%) had hemophilia B and 28 (12.4%) were antibody positive compared to 9 (7%) in vWD. Co infection of HBV was only found in hemophilia A with a prevalence of0.5%.Of those with hemophilia A, 515 (86.6%) had severe hemophilia. Thirty two(32.32%) cases of hemophilia A had acquired HCV infection after 1996 (after introduction of HCV screening in blood banks in Iraq) and there was a statistically significant association with treatment by factor VIII only. **Conclusions:** The prevalence of HCV in patients with inherited bleeding disorder is (13.2%). Since no independent risk factor was found in this high risk group, it can be concluded that multitransfusion is the only predictor for HCV infection. Anti-HCV antibody positivity was associated with the age at diagnosis of hemophilia, type of treatment and presence of inhibitory antibodies but not with the type of hemophilia, the severity of the disease nor positivity to HBV.
Keywords: Hepatitis C virus, hemophilia, bleeding disorders.

1. Introduction

HCV infection is considered as an important health problem, worldwide. It is estimated that 130- 150 million people globally have chronic hepatitis C infection(1)and it results in 350000- 500000 deaths annually from infected individuals.(1,2)It is the most important cause of morbidity and mortality in multiply transfused patients due to inherited bleeding disorders. Most of the patients with mentioned disease have been infected during receiving clotting factors before the introduction of virus-inactivation methods.(3)Most asymptomatic blood donors found to have anti-HCV and about 20–30% of persons with reported cases of acute hepatitis C do recall risk-associated behaviors when questioned carefully. Hepatitis C can be transmitted by injection drug use, occupational exposure to blood, and the likelihood of infection is increased in hemodialysis units. As a blood borne infection, the chances of sexual and perinatal transmission have been estimated to be about 5%,both of these modes of transmission are inefficient for hepatitis C. Sexual transmission appears to be confined to persons with multiple sexual partners and sexually transmitted diseases. Health workers are more likely to acquire HCV infection through accidental needle punctures, the efficiency of which is about 3%. (4)

Evidences indicated that the risk of acquisition of HCV infection is higher in hemophiliacs than patients with other inherited bleeding disorders. HCV seropositivity was significantly associated with longer history of transfusion. Advances in factor replacement therapy and management of the disease especially appropriate treatment of infectious diseases led to improvement in the overall life expectancy and quality of life of hemophiliacs. HCV infection is considered one of the challenging factors they face due to its related complications such as increased risk of developing end-stage liver disease and hepatocellular carcinoma.(5)Infection with HCV can result in both acute and chronic hepatitis. The acute process is most often asymptomatic; or symptoms abate within a few weeks. Acute infection rarely causes hepatic failure. The risk of chronic infection is high. In most studies, 80 to 100 percent of patients remain HCV (RNA) positive, and 60 to 80 percent have persistently elevated liver enzymes. (6)

Unfortunately, HCV successfully evades the host immune response in 55% to 85% of acutely infected persons, thus leading to chronic infection. Chronic HCV infection can leads to cirrhosis and hepatocellular carcinoma. The incidence of these complications has risen dramatically in the 2000s but is expected to decline over the next 20 years. Complications of HCV-related cirrhosis are currently the leading indication for liver transplantation in the United States and Europe.(7)

Chronic HCV infection is usually slowly progressive and may not result in clinically apparent liver

disease in many patients if the infection is acquired later in life. Approximately 20 to 30 percent of chronically infected individuals develop cirrhosis over a 20- to 30-year period of time.[8]

The mechanism responsible for the high prevalence of chronic infection is unclear. It may be related to the genetic diversity of the virus and its tendency toward rapid mutation, allowing HCV to escape immune recognition. [9]Survival is decreased in patients with HCV, especially in those who have developed cirrhosis. [10]

Early diagnosis and treatment of HCV infection among patients with inherited bleeding disorders is required, because the response to treatment reduces with age.[11] Hepatitis C status was defined as "spontaneous clearance" (positive anti-HCV antibodies but negative HCV RNA tests on at least 2 occasions at least 6 months apart), or "chronic hepatitis C" (positive anti-HCV antibodies and persistently positive HCV RNA).[12]

This study aimed to evaluate the prevalence of (HCV) infection and determine potential risk factors among patients with inherited bleeding disorders.

2. Patients and Methods

2.1 Study design and sample selection

This is a cross sectional retrospective study carried out in the Hemophilia unit in Children Welfare Teaching Hospital, Medical city in Baghdad/ Iraq during a period between 1st of June 2014 to 1stof January 2015. This study involved all patients with inherited bleeding disorders including hemophilia A&B, von Willebrand disease, thrombosthenia, hypofibrinogenemia, and deficiency of factors (VII, X and XIII); of all ages who were registered in this ward.

2.2 Clinical and laboratory evaluation

Demographic and virological data from 1158 patients were surveyed and analyzed. Testing for HCV antibody using ELISA test (third generation) and for HBs Ag was performed in the local hospital laboratories at baseline and every 6 months. So those test results were extracted from patient records. The level of severity of hemophilia A was determined depending on the amount of clotting factor that is missing from a person's blood as shown in the following table:

Table (1): hemophilia A severity

Level	Percentage of normal factor activity in blood	Number of international units (IU) per milliliter (ml) of whole blood
normal range	50%-150%	0.50–1.5 IU
mild hemophilia	5%-40%	0.05–0.40 IU
moderate hemophilia	1%-5%	0.01–0.05 IU
severe hemophilia	less than 1%	less than 0.01 IU

Hemophiliacs were classified into mild, moderate and severe cases accordingly[13].Generally, hemophiliacs were treated with FVIII and FIX concentrates alone or with factor, blood products and whole blood. Patients after being diagnosed with HCV infection were referred to the GIT centre for further management.

2.3 Statistical analysis

Minitab 17 program package were used to analyze the data, Anderson-Darling test were used to test normality of data. Median of data and inter quartile range (IQR) were used to described the data. A non-parametric method were used to assess the statistical significance between variable, Kruskal- Wallis test was used to test the equality of medians for two or more variables, while Mann-Whitney test was used to test the equality of two population medians, and calculate the corresponding p- value. Data were presented using bar when presenting prevalence. All data were considered significant when p- value was less than 0.05.

3. Results

Medical records of 1158 patients with inherited bleeding disorders were analyzed. Of total, 153 patients were HCV antibody positive with a prevalence of 13.2% as shown in figure (1).

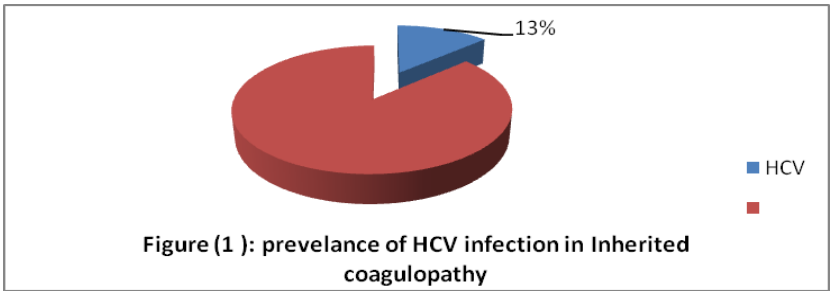

Figure (1): prevelance of HCV infection in Inherited coagulopathy

Table (2) shows that from total sample, 595 (51.4%) were cases with hemophilia A, 225 (19.4%) with hemophilia B, 128 (11.1%) with vWD, and 100 (8.6%) with thrombosthenia in addition to other inherited factors deficiencies shown in the table. Of 153 patients who were infected with HCV,99 (64.7%) were cases of hemophilia A and 28 (18.3%) of hemophilia B.

Table (2): The frequency of HCV infection among the study group

variables	all patients		HCV	
	no	Percent %	No	Percent %
Hemophilia A	595	51.4	99	64.7
Hemophilia B	225	19.4	28	18.3
vWD	128	11.1	9	5.9
Thrombosthenia	100	8.6	2	1.3
F VII deficiency	35	3.0	5	3.3
F XIII deficiency	34	2.9	2	1.3
Hypofibrinogenemia	32	2.8	4	2.6
F X deficiency	9	0.8	4	2.6
Total	**1158**	**100**	**153**	**100**

The prevalence of HCV infection was 16.6% in hemophilia A, 12.4% in hemophilia B, in 7% in vWD, as shown in figure (2).

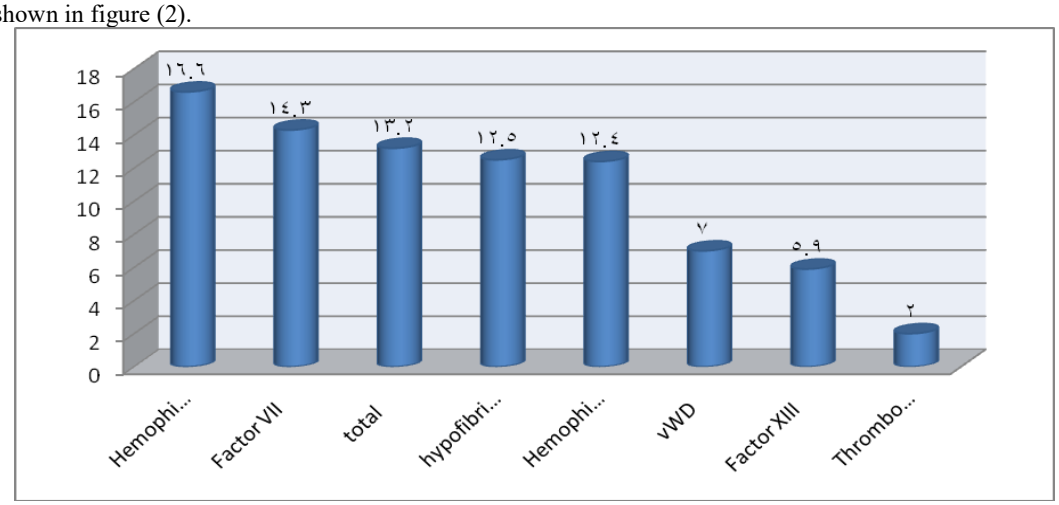

Figure (2): The prevalence of HCV infection in the study group.

Data distribution.

Since most of the data did not follow normal distribution, non-parametric methods were used to assess the variation in median of data. Median and Interquartile Range (IQR) were selected to present the data.

Median age (IQR) of patients having hemophilia B, hemophilia A, and vWD was: 31 (10.5), 24 (11.5), 19 (23) respectively. Median age at the diagnosis of HCV of patients with hemophilia A, B and vWD was almost the same (10 y) as shown in table (3). Co infection of HBV with HCV was only found in 2 patients with hemophilia A with a prevalence of 0.5%.

Of all patients with hemophilia A with hepatitis, 515 (86.6%) patients showed severe factor VIII deficiency while 80 (13.4%) patients had moderate deficiency. Of those with hemophilia B with hepatitis, 201 (89.3%) showed severe factor VIII deficiency while 24 (10.71%) patients had moderate deficiency without a statistically significant difference (P- value =1).

Factor VIII inhibitors were found in 116 (19.6%) of cases of hemophilia A while none of cases of hemophilia B showed positive to factor IX with a statistically significant difference (P- value <0.001).

Table (3): Distribution of patient's characteristics.				
Variable	Hemophilia A	Hemophilia B	vWD disease	P- value
Current Age/ y Median (IQR)	24 (11.5)	31 (10.5)	19 (23)	0.065
Age/y at diagnosis of HCV Median (IQR)	10 (6.5)	9 (7.8)	10 (11)	0.098
HBV co infection *	2 (0.5%)	-	-	
Severe deficiency (VIII)/ No.(%)	515 (86.6%)	201 (89.3%)	-	1
Moderate deficiency (VIII)/ No.(%)	80 (13.4%)	24 (10.71%)	-	
VIII Inhibitor	116 (19.6%)	-	-	<0.001
IX Inhibitor	-	0	-	
* Frequency of HBV in the study group= 0.259%				

Studying the effect of treatment type (factor VIII + blood product vs. factor only), and age at diagnosis of hemophilia A on infection with HCV, showed a relationship between type of treatment and development of infection with HCV when holding age at diagnosis constant with a statistically significant difference (p- value of 0.03), while age did not display such relationship.

For patients who were treated with blood product and factors, the negative coefficient of -1.43 and the odd ratio (OR) of 0.24 indicate that those subjects tend to have a higher HCV infection rate than subjects who were treated with factors only. Given that subjects have the same age at diagnosis of hemophilia A, the OR can be interpreted as the odd of patients taking blood products having no infection with HCV being 24% of the odd of patients taking only factors having no HCV infection as shown in table (4).

Table (4): Binary log regression of treatment type vs. age at diagnosis of hemophilia A and infection with HCV			
Predictor	Correlation coefficient	P- value	OR**
Treatment *	-1.43	0.03	0.24
Age at diagnosis	-0.005	0.971	0.99
Treatment*: factor + blood product vs. factors only. OR** : odd ratio			

As shown in table (5), treatment type did not affect the number of years to get HCV infection from time of diagnosis of hemophilia A (p- value of 0.433); while age at diagnosis of hemophilia showed an effect on number of years to get HCV infection in hemophilia A with a statistically significant difference (p- value of 0.024). This means that the younger the patient the highest the possibility to get HCV infection.

The negative coefficient and an OR less than 1 indicate that as hemophilia A patients diagnosed younger the highest the possibility to get HCV infection when holding the effect of treatment type constant.

Table (5): Ordinal log regression of duration in years from diagnosis of hemophilia A to diagnosis of HCV vs. treatment type and age at diagnosis of hemophilia A.			
Predictor	Correlation coefficient	P- value	OR
Treatment *	0.29	0.433	1.34
Age at diagnosis of hemophilia A	-0.26	0.024	0.77
Treatment*: factor + blood product vs. factors only. OR** : odd ratio			

As shown in table (6), 32 (32. 32%) cases of hemophilia A who were HCV positive had acquired HCV infection after 1996, it means after introduction of screening for HCV in blood donors in Iraq.

Table (6): Distribution of cases of hemophilia A&B and vWD patients according to period of positivity of HCV (before or after 1996).		
Variable	**Count**	**Percentage**
Hemophilia A		
Before 1996	67	67.68
After 1996	32	32.32
Hemophilia B		
Before 1996	24	85.71
After 1996	4	14.29
vWD		
Before 1996	2	22.22
After 1996	7	77.78

Only patients with hemophilia A show a statistically significant association between period of diagnosis of HCV infection whether before or after 1996 and treatment received; the value of correlation coefficient (0.375) indicate a fair degree of relationship and was negative correlation, as shown in table (7).

Table (7): Association between diagnosis before or after 1996 and type of treatment received in HCV positive cases among patients with hemophilia A and B.

Variable	Blood products & factors		Factors only		p value	Spearman rho correlation
	No	%	No	%		
Hemophilia A						
After 1996	5	11.90	27	47.37	0.0002*	-0.374743
Before 1996	37	88.10	30	52.63		
Hemophilia B						
After 1996	0	0	4	17.39	1	-0.190347
Before 1996	4	100	19	82.61		
* Significant differences						

4. Discussion

HCV infection is considered as an important issue among patients with inherited bleeding disorders but studies showed that the rate of infection is higher in hemophiliacs because of the frequent use of blood products and improving the life expectancy of the disorder, so in this research we aimed to determine HCV infection rate and associated risk factors mainly among those patients.

In the present study, 127 (15. 48%) hemophiliacs (type A& B) had antibody to (HCV). Various studies among multi-transfused hemophilia patients demonstrated a wide range of prevalence of transfusion-transmitted infections. The prevalence of HCV infection in Iran ranged between 29%-83.3% in different cities or province of Iran. The lowest rate was in Zahedan and the highest in Tehran.[6,14- 16]The rate of HCV infection in one study in Brazil was42.2%.[17]It was lower in Pakistan (36%). [18]

In a study done in Bosnia, HCV infection was positive in 38.7% of cases of hemophilia and infected hemophiliacs with HCV and HBV was found in 4%.[3]

In Netherlands it was found to be (68%).[19]Studies from some neighboring Arabic countries reported an HCV infection rate of 29.4% to 79% among multi- transfused patients.[20, 21] A study done in Egypt showed that HCV prevalence among multi-transfused patients ranged between 10-55%.[22]

Other studies showed lower rates of infection. Central and East Asia and North Africa/Middle East are estimated to have a prevalence (>3.5%); South and Southeast Asia, sub-Saharan Africa, Andean, Central, and Southern Latin America, Caribbean, Oceania, Australasia, and Central, Eastern, and Western Europe have a prevalence (1.5%-3.5%); whereas Asia Pacific, Tropical Latin America, and North America have very low prevalence (<1.5%).[23]The difference observed in different populations may be due to laboratory methods and selection methods.

In the present study, the overall prevalence of HCV infection among cases of inherited coagulopathy was 13.2%which is considered very high because in Iraq hepatitis C is considered of low endemicity with a rate of 0.5% in blood donors[24,25]compared with other countries. WHO estimated a prevalence rate for HCV infection of about 4.6% in Eastern Mediterranean in 1999. Egypt had the largest scale ranging from 6% to 28%. The prevalence rates reported were 1.8% in Turkey and 2.2% in the Gaza Strip. [26]

This different in prevalence of HCV infection attributed to different epidemiological distribution and risk factors of HCV infection between these countries.

The prevalence of HCV infection in blood donors in a another study done in Iraq (Baghdad) between 2006 – 2009), was found to be 0.3% in all donors.[27] This indicates that blood product is important predisposing factor to get HCV infection despite the extensive screening and disinfection procedure done in our country.

This could be attributed to the fact that multiple use of the same person over time to blood products in their life lead to that increased cumulative risk to get HCV infection as shown by **Yazdani et al** who found that only multitransfusion is independently associated with HCV infection.[28]

In Iraq anti- HCV ELISA (third generation) is the only screening test for detection of HCV infection in all blood donors. After exposure to HCV, anti-HCV antibodies can be detected by ELISA in 50 to 70% of the patients at the onset of symptoms, this percentage increasing to approximately 90% after 3 months and the remaining 10% may take even longer, despite the presence of viremia in acute infections.[29]

The chances of false negativity and false positivity are not uncommon like other antigen-antibody dependent reactions. In early phase of acute HCV infection there is a window period in which the antibodies have not yet reached the detectable level by ELISA and hence the ELISA tests are falsely negative despite the viremia.[30]False positive ELISA tests are also not uncommon.[31]

False positive ELISA for anti HCV can be seen in patients who have cleared the virus after acute infection or by therapy and as such may be positive on ELISA which may indicate past infection. [32]

In low-risk populations, such as blood donors, or in random population screening negative ELISA results are sufficient to rule out the presence of HCV. However, false-positive results can occur in these

populations. In such cases, a qualitative study of HCV RNA should be performed to confirm the diagnosis.[29] In high-risk populations, when there is clinical suspicion of HCV infection, positive ELISA results confirm the exposure to HCV. A qualitative study of HCV RNA should be performed to distinguish individuals with chronic infection from those who have eliminated the HCV spontaneously. [33]

To evaluate which factor leads to this increased prevalence of HCV infection in hemophilic patients; we studied hemophilia A patients and use logistic regression analysis. We did not find any independent risk factor for hepatitis C infection and it seems that multitransfusion is the most important risk factor in this regard. Our results were similar to the results of **Mojtabavi** *et al,* in Isfahan and some other studies in Iran and other countries.[5,35] Where as others have indicated the role of other factors such as age.[17]

In the present study, age at diagnosis of hemophilia showed an effect on number of years to get HCV infection in hemophilia A with a statistically significant difference (p- value of 0.024). This means that the younger the patient the highest the possibility to get HCV infection compared to late age at diagnosis when holding the effect of treatment type constant; this could be attributed to the fact that as the patient diagnosed younger he get the highest chance to use more multiple transfusion during his life span and more chance to get HCV infection.

In the present study; HBV infected individual were 0.259% in total coagulopathy population and were all in hemophilia A group with a prevalence of 0.5% as co infection with HCV. In a study by **Mojtabavi et al**[35] prevalence of HBV infection was (0.4%) and (0.2%) for co infection, while Zhubi et al [3]found a higher HBV co-infection (2.7%). These low numbers indicate the active policy of vaccination of individual at risk with HBV vaccine and mandatory blood screening that had this major impact on low prevalence of HBV infection.

The present study showed a statistically significant difference in median current age between hemophilia A and B with (p- value = 0.0203), but prevalence of (HCV) infection was not statistically associated with the severity of factor VIII deficiency. Similar results were found in a study done in Brazil by **Santanna LPet al**. [17] Antibody to hepatitis C virus was discovered in late 1987.[14] In Iraq, viral hepatitis prevention and control program was started during early seventies and screening blood donors for HCV was introduced in Iraq in 1996.[15]

The present study showed that 32 (32. 32%) cases of hemophilia A had acquired HCV infection after 1996 and there was a statistically significant association with treatment by factor VIII only rather than combination of factor and whole blood transfusion. So in spite of screening method for HCV in blood banks still there is risk of getting infection during transfusion methods from paramedics or equipments. We recommend implementing blood safety strategies, donor selection and quality assured screening of all donated blood and blood components as well as strengthening of infection control precautions in health care centers and community settings to prevent viral hepatitis infection.

5. Conclusions.

The prevalence of HCV in patients with inherited bleeding disorder is (13.2%). Since no independent risk factor for hepatitis C disease was found in this high risk group, it can be concluded that multitransfusion is the only predictor for hepatitis C. Anti-HCV antibody positivity was associated with the age at diagnosis of hemophilia, type of treatment and presence of inhibitory antibodies but not with the type of hemophilia, the severity of the disease nor positivity to HBV.

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