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Research Article

THE PREVALENCE OF HEPATITIS C VIRUS INFECTION AND POTENTIAL RISK FACTORS AMONG MULTIPLY TRANSFUSED PATIENTS

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ABSTRACT

Objective: Patients who frequently receive blood have high risk of hepatitis C virus (HCV) infection. This study aimed to evaluate the prevalence of HCV infection and potential risk factors among multiply transfused patients.

Methods: A cross-sectional retrospective study was conducted in the hemophilia unit in Medical City in Baghdad, between June 1, 2016, and January 1, 2017. After taking consents and approval of ethical comity, the medical records of 1158 patients with hemophilia A and B, von Willebrand disease (vWD), thrombasthenia, Factors VII, X, and XIII deficiencies, and hypofibrinogenemia were analyzed for the presence of HCV antibody using (enzyme-linked immunosorbent assay). Cases of hemophilia were classified into mild, moderate, and severe.

Results: The 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. Of those with hemophilia A, 515 (86.6%) had severe hemophilia, and 32 (32.32%) cases had acquired HCV infection after 1996 (after introduction of HCV screening in blood banks in Iraq). There was a statistically significant association with treatment by Factor VIII only.

Conclusion: The prevalence of HCV in patients with inherited bleeding disorder is 13.2%. In this study, it was found that multitransfusion is the only predictor for HCV infection in this group of patients.

Keywords: Hepatitis C virus, Multitransfusion, Prevalence.

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INTRODUCTION

Hepatitis C virus (HCV) infection is considered as an important health problem, worldwide. It is the most important cause of morbidity and mortality in multiply transfused patients due to inherited bleeding disorders [1,2]. Most asymptomatic blood donors were found to have anti-HCV antibodies and about 20–30% of persons with reported cases of acute hepatitis C do recall risk- associated behaviors when questioned carefully [3].

Evidence indicated that the risk of acquisition of HCV infection is higher in hemophiliacs than patients with other inherited bleeding disorders. In most studies, 80–100% of patients remain HCV (RNA) positive, and 60–80% have persistently elevated liver enzymes [4]. Unfortunately, HCV successfully evades the host immune response in 55–85% of acutely infected persons, thus leading to chronic infection which can lead to cirrhosis and hepatocellular carcinoma [5,6].

Early diagnosis and treatment of HCV infection among patients with inherited bleeding disorders is required because the response to treatment reduces with age [7].

This study aimed to evaluate the prevalence of HCV infection and determine potential risk factors among multiply transfused patients.

METHODS

Study design

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 June 1, 2016, and January 1, 2017. This study involved all patients with inherited bleeding disorders including hemophilia A and B, von Willebrand disease (vWD), thrombasthenia, hypofibrinogenemia, and deficiency of factors (VII, X, and XIII); of all ages who were registered in this ward. Demographic and virological data from 1158 patients were surveyed and analyzed. Testing for HCV antibody using enzyme-linked immunosorbent assay (ELISA) test (third generation) was performed in the local hospital laboratories at baseline and every 6 months. Hence, 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 Table 1.

Hemophiliacs were classified into mild, moderate, and severe cases accordingly [8]. In general, 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 gastrointestinal center for further management.

Statistical analysis

Minitab 17 program package was used to analyze the data, Anderson-Darling test was used to test normality of data. Median of data and interquartile range (IQR) were used to describe the data. A non-parametric method was used to assess the statistical significance between variables, Kruskal–Wallis test was used to test the equality of medians for two or more variables, while Mann–Whitney U-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 *$p<0.05$ and highly significant when **$p<0.001$.

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 Fig. 1.

Table 1: Hemophilia A severity

Level	Percentage of normal factor VIII activity in blood (%)	Number of IUs 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	<1	<0.01 IU

IUs: International units

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

Variables	All patients number (%)	HCV number (%)
Hemophilia A	595 (51.4)	99 (64.7)
Hemophilia B	225 (19.4)	28 (18.3)
vWD	128 (11.1)	9 (5.9)
Thrombasthenia	100 (8.6)	2 (1.3)
Factor VII deficiency	35 (3.0)	5 (3.3)
Factor XIII deficiency	34 (2.9)	2 (1.3)
Hypofibrinogenemia	32 (2.8)	4 (2.6)
Factor X deficiency	9 (0.8)	4 (2.6)
Total	1158 (100)	153 (100)

vWD: Von Willebrand disease, HCV: Hepatitis C virus

As shown in Table 2, 595 (51.4%) were cases with hemophilia A, 225 (19.4%) with hemophilia B, and 128 (11.1%) with vWD. Of 153 patients who were infected with HCV, 64.7% were cases of hemophilia A and 28 (18.3%) of hemophilia B.

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

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 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 the patients with hemophilia A, B, and vWD was almost the same (10 years) as shown in Table 3.

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=1).

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

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=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 odds 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 odds of patients taking blood products having no infection with HCV being 24% of the odds of patients taking only factors having no HCV infection as shown in Table 4.

As shown in Table 5, treatment type did not affect the number of years to get HCV infection from time of the diagnosis of hemophilia A, while age at diagnosis of hemophilia showed a statistically significant effect. The negative coefficient and an OR <1 indicate that as hemophilia

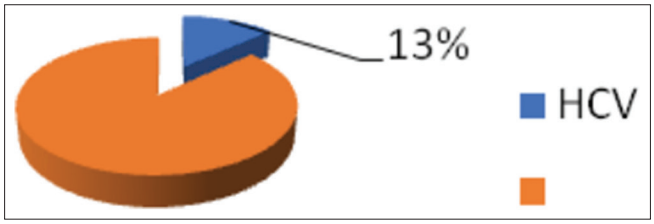

Fig. 1: Prevalence of hepatitis C virus infection in inherited coagulopathy

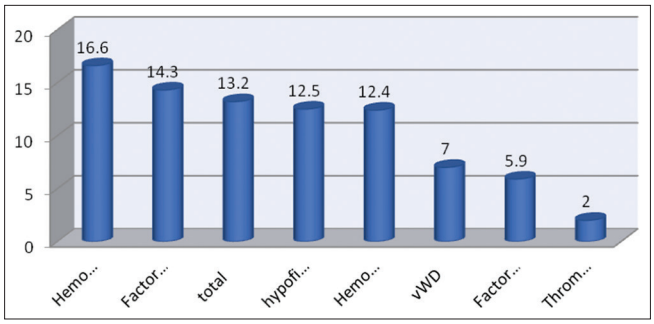

Fig. 2: The prevalence of hepatitis C virus infection in the study group

A patients diagnosed younger the highest the possibility to get HCV infection when holding the effect of treatment type constant.

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 the introduction of screening for HCV in blood donors in Iraq.

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

DISCUSSION

In the present study, 127 (15.48%) hemophiliacs (type A and B) had antibody to HCV. Various studies among multiply transfused hemophilia patients demonstrated a wide range of prevalence of the transfusion-transmitted infections. The prevalence of HCV infection in Iran ranged between 29% and 83.3% in different cities or province of Iran. The lowest rate was in Zahedan and the highest in Tehran [4,9-11]. The rate of HCV infection in one study in Taiwan was 45.7% [12]. It was lower in Pakistan (36%) [13].

In the Netherlands, it was found to be 68% [14]. Studies from some neighboring Arabic countries reported an HCV infection rate of 78.6% among multitransfused patients [15,16]. A study done in Egypt showed that HCV prevalence among multitransfused patients ranged between 10% and 55% [17].

Although patients with thalassemia were not included in this study, it is wise to mention that the prevalence of HCV in a study in India was 18.70% (320 of 1711 patients with thalassemia) [18].

Table 3: Distribution of patient's characteristics

Variables	Hemophilia A	Hemophilia B	vWD▪disease	p
Current age/year median (IQR)	24 (11.5)	31 (10.5)	19 (23)	0.065
Age/year at Dx. of HCV median (IQR)	10 (6.5)	9 (7.8)	10 (11)	0.098
Severe deficiency (VIII)/number (%)	515 (86.6)	201 (89.3)	-	1
Moderate deficiency (VIII)/number (%)	80 (13.4)	24 (10.71)	-	
VIII inhibitor (%)	116 (19.6)	-	-	<0.001**
IX inhibitor	-	0	-	

▪Von Willebrand disease, **Highly significant difference. vWD: Von Willebrand disease, IQR: Interquartile range, HCV: Hepatitis C virus

Table 4: Binary log regression of treatment type versus age at diagnosis of hemophilia A and infection with HCV

Predictor	Correlation coefficient	p	OR**
Treatment*	−1.43	0.03	0.24
Age at diagnosis	−0.005	0.971	0.99

Treatment*: Factor+blood product versus factors only. OR**: Odds ratio, HCV: Hepatitis C virus

Table 5: Ordinal log regression of duration in years from diagnosis of hemophilia A to diagnosis of HCV versus treatment type and age at diagnosis of hemophilia A

Predictor	Correlation coefficient	p	OR**
Treatment*	0.29	0.433	1.34
Age at diagnosis of hemophilia A	−0.26	0.024	0.77

Treatment*: Factor+blood product versus factors only. OR**: Odds ratio, HCV: Hepatitis C virus

Table 6: Distribution of the cases of hemophilia A and B and patients with vWD according to the period of positivity of HCV (before or after 1996)

Variable	Count (%)
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)

*Von Willebrand disease. vWD: Von Willebrand disease, HCV: Hepatitis C virus

Other studies showed lower rates of HCV infection. Central and East Asia and North Africa/Middle East are estimated to have a prevalence (>3.5%, 3.5%), whereas Asia Pacific, Tropical Latin America, and North America have very low prevalence (<1.5%) [19]. 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 [20,21] compared with other countries. In studies reporting HCV prevalence among hemophiliacs in the Maghreb countries, the highest prevalence was reported in Libya 94%, while it was 30% in Algeria, and was 42% in Morocco [22].

This difference in the 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 another study done in Iraq (Baghdad) between 2006 and 2009 was found to be 0.3% in all donors [23]. 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 leads 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 [11].

In Iraq, anti-HCV ELISA (third generation) is the only screening test for the detection of HCV infection in all blood donors. After exposure to HCV, anti-HCV antibodies can be detected by ELISA in 50–70% of the patients at the onset of symptoms, this percentage increased to approximately 90% after 3 months and the remaining 10% may take even longer, despite the presence of viremia in acute infections [24].

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. False positive ELISA tests are also not uncommon [25,26]. 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 [27].

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 [28].

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 [29]. While in Jang *et al.* study, there was a significant association of age with anti-HCV seropositivity by logistic regression analysis (odds ratio/95% confidence interval [OR/CI]: 1.12/1.07–1.18, p<0.001) [12].

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=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 gets the highest chance to use more multiple transfusion during his life span and more chance to get HCV infection.

The present study showed a statistically significant difference in median current age between hemophilia A and B with p=0.0203, but the prevalence of HCV infection was not statistically associated with

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 and factors n (%)		Factors only n (%)		p	Spearman rho correlation
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		

**Highly significant difference. HCV: Hepatitis C virus

the severity of factor VIII deficiency. Similar results were found in a study done by Jang *et al*. [12]. Antibody to HCV was discovered in late 1987 [9]. In Iraq, viral hepatitis prevention and control program were started during early seventies and screening blood donors for HCV were introduced in Iraq, in 1996 [10].

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. Hence, in spite of screening method for HCV in blood banks, still there is a risk of getting infection during transfusion methods from paramedics or equipment. 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.

CONCLUSION

In this study, the prevalence of HCV in patients with inherited bleeding disorder was 13.2%. It was found that multitransfusion is the only predictor for HCV infection in this group of patients. 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 nor the severity of the disease.

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AUTHORS' CONTRIBUTION

Concept, collection of data, and writing the article - Manal Khudder Abdul Razak.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

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