Prevalence of hepatitis C in children with congenital bleeding disorders in Upper Egypt: a cross-sectional study

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Introduction
Congenital bleeding disorders are a heterogeneous group of hemorrhagic disorders that are mainly treated with blood products. Transfusion caused a large number of hepatitis C virus (HCV) infections, until systematic screening of blood supplies was initiated.

Patients and methods
This was a cross-sectional study that included 100 patients with congenital bleeding disorders who received a blood product (at least 3 months before HCV antibody testing) and underwent full clinical evaluation besides the following investigations: full blood count, liver function tests, HCV antibody by enzyme immunoassay, and if enzyme immunoassay was positive, HCV-PCR was requested.

Results
Two patients were positive for anti-HCV antibodies. HCV-PCR results for both were also positive. Both patients were in late adolescence (about 18 years). No significant rise of liver enzymes (alanine aminotransferase, aspartate aminotransferase) was noted in any patient of the study group.

Conclusion
Methods of screening blood products including (recent use of nucleic acid testing for blood donors) were highly effective in preventing hepatitis C infection.

Keywords:
congenital bleeding disorders, hepatitis C, pediatric, prevalence

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Introduction

Congenital bleeding disorders (CBD) are a heterogeneous group of hemorrhagic disorders with highly variable incidence, clinical presentations, and laboratory findings [1]. The discovery of hepatitis C virus (HCV), in blood transfused patients, led to the development of diagnostic tools and, in the early 1990s, the implementation of systematic screening of blood supplies; in the USA this contributed to the reduction of infection via blood transfusion by almost 100% [2]. HCV infection became a major health problem worldwide. A recent study based on anti-HCV seroprevalence data have estimated that 185 million people corresponding to 2.8% of the world's population have been infected with HCV [3]. Among those infected with HCV, the WHO estimates that 130–150 million individuals worldwide are chronically infected [4]. Any source of blood is able to transmit the virus, even if it is indirect. Spontaneous viral clearance occurs in about 25% of individuals, generally in the first 3–6 months of infection [5]. Despite the great successes achieved in the fields of virology and diagnostics, several difficulties interfere with HCV infection control and eradication. New HCV infections still occur, especially in some of the poorest regions of the world [3]. With the advent of highly active direct-acting antivirals to treat chronic hepatitis C, the goal of worldwide eradication of hepatitis C infection seems achievable. However, a major challenge in reaching that goal is the high rate of underdiagnosis [6].

Individuals who qualify for HCV testing should be tested for HCV antibodies and, if positive, this should be followed by a confirmatory HCV-RNA test [7]. As the anti-HCV reactivity by screening assays can indicate a past infection, acute, or chronic hepatitis [8]. HCV enzyme immunoassay have a sensitivity of about 98% and specificity of about 99% [9].

Aim

This study aimed to estimate the frequency of HCV infection in pediatric patients with CBD (who received any blood product) to assess the magnitude of the problem.

Patients and methods

The study included 100 patients with known CBD attending the hematology unit in Assiut University Children Hospital from April 2018 to March 2019. Their ages ranged from 8 months to 18 years, 68 men and 32 women.

Inclusion criteria

(1) All patients with CBD with a history of receiving any blood product.

Exclusion criteria

(1) Patients with acquired bleeding disorders.
(2) As HCV antibodies are typically not detectable until 2 months or longer after acquisition of infection [10], any transfusion in the last 3 months prior to HCV antibody testing was not considered.

Statistical analysis

Data were processed and analyzed using the IBM SPSS 20.0 software (IBM Corp., Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD (range) while nominal data were expressed in the form of frequency (percentage).

Ethical consideration

The study was approved by the Ethics Committee of Faculty of Medicine at Assiut University. Informed consent was obtained for all participating patients.

The parameters to be assessed

Frequency of positive anti-HCV antibodies and of positive HCV-PCR.

Results

Table 1 demonstrates the characteristics of the studied patients and frequency of use of each type of blood product. The study included 100 patients with a diagnosis of CBD. The number of men was about as twice as women, with about one-third of patients with a positive family history of the same disorder. Regarding transfusion history: most patients were transfused less than or equal to 10 times. The most common bleeding form was bleeding after trauma or circumcision, found in about two-thirds of patients.

Table 2 demonstrates gender distribution and family history for the most common diagnoses.

The most common diagnoses were hemophilia A, Von Willebrand disease (VWD), and thrombasthenia.

Table 1 Characteristics of the studied patient and frequency of usage of each type of blood product

	n (%)
Age	
Range	8 months to 18 years
Mean±SD	8.1±4.7
Age of first transfusion	
Range	0.5-14 years
Mean±SD	6±2.9 years
≤5 years	35 (35)
5-10 years	36 (36)
10-18 years	29 (29)
History	
Male	68 (68)
Female	32 (32)
Positive family history	36 (36)
Bleeding manifestation	
After trauma or circumcision	66 (66)
Joint bleeding	7 (7)
Cutaneous bleeding	46 (46)
Orificial bleeding	60 (60)
GI bleeding	8 (8)
Frequency of transfusion	
≤5 times	46 (46)
6-10 times	32 (32)
>10 times	22 (22)
Product type	
Factor concentrate	43 (43)
Fresh frozen plasma	27 (27)
Platelet-rich plasma	20 (20)
Cryoprecipitate	14 (14)
Packed RBCs	13 (13)
Platelet concentrate	12 (12)

GI, gastro intestine; RBC, red blood cell.

The observed ratio of men to women was around 1: 1.5 in VWD, thrombasthenia, fibrinogen disorders, and Fanconi anemia. On the other hand, all patients with hemophilia A or B were men. Positive family history ranged from 62.5% in hemophilia to 11.1% in fibrinogen disorders and 10% in Fanconi anemia.

High transfusion frequency was noted in Fanconi anemia with 80% of patients were transfused greater than 10 times. Low transfusion frequency was noted in VWD and thrombasthenia with 66.7 and 70.6% of patients requiring transfusion less than or equal to 5 times in these disorders, respectively.

All patients were screened for liver disease using liver function tests and HCV-Ab by enzyme immunoassay, only two were found positive; a male patient with hemophilia A who had a history of frequent transfusion of factor VIII concentrate and history of operation in which he received PRBCs, and the second patient was a female with congenital thrombocytopenic purpura with a history of receiving blood transfusion every 2 months. HCV-PCR results for both were also positive. Rises of liver enzymes (alanine

Table 2 Sex distribution and family history for the most common diagnoses

History	Hemophilia (*n*=48) [*n* (%)]	Thrombasthenia (*n*=17) [*n* (%)]	VWD (*n*=12) [*n* (%)]	Fibrinogen disorders (*n*=9) [*n* (%)]	Fanconi anemia (*n*=10) [*n* (%)]
Sex					
Male	48 (100)	7 (41.2)	5 (41.7)	4 (44.4)	4 (40)
Female	0	10 (58.8)	7 (58.3)	5 (55.6)	6 (60)
Positive family history	30 (62.5)	2 (11.7)	2 (16.7)	1 (11.1)	1 (10)

VWD, Von Willebrand disease.

Table 3 Laboratory data of the studied patients regarding liver function tests and full blood count

Investigation	Range	Mean
WBCs	1.5-19	7.4±3.3
Hemoglobin	4-13	7.2±2.1
Platelets	13-665	299±188
ALT	12-88	40±18
AST	15-100	60±38
Total bilirubin	0.1-0.8	0.2±0.2
Albumin	1.3-4.9	2.5±1.6

ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cells.

aminotransferase, aspartate aminotransferase) were mild (according to Common Terminology Criteria for Adverse Events) [11] or absent (Table 3). Another finding was hypoalbuminemia, found in several patients. The leading causes were sepsis, heart failure, and malnutrition.

Discussion

Male-to-female ratio was about 2:1; this can be explained by the large proportions of patients with hemophilia A and B (48%) that are X-linked disorders that affect mainly the male offspring. Al-Rahal [12], however, reported that the male-to-female ratio was 1.1:1. This can be explained by the low frequency of hemophilia in his patients. In our study, only 36% of patients had a positive family history, which can be explained by the high frequency of acquired mutations that are responsible for congenital disorders, and by that the patients have shorter survival and lesser chance to reproduce.

Variation in frequency of transfusion is attributed to several factors, most importantly age, type, and severity of the disease in addition to the used treatment regimen/protocol. The wide range for age of first transfusion is mainly due to the variation in type and severity of the disease. Older ages were noted primarily in VWD where menorrhagia after puberty was a common presenting problem. Regarding bleeding manifestations, the most common presenting symptom was bleeding following male circumcision or trauma. This agrees with Al Tonbary *et al.* [13]. Male circumcision is an extremely common practice in young children in our locality due to religious and cultural reasons. In many instances, it is the first trauma that challenges the hemostatic functions of the child. On the contrary, Al-Rahal [12] reported that the most common type of bleeding was ecchymosis (30.6%), possibly due to the low frequency of hemophilia in his patients.

Hepatitis C markers were positive in only two (2%) patients. This number is lower compared with Al Tonbary *et al.* [13], who reported that 11.1% of participants were HCV PCR positive. The low frequency in our study can be explained by the relatively improved screening and handling of blood products over years and the use of nucleic acid testing. Kandeel *et al.* [14] reported that in Egyptian children, 1–14 years old, the prevalence of HCV antibody and HCV RNA were 0.4%. He also reported that there was an overall significant reduction of 32 and 29% in the prevalence of HCV antibody and HCV RNA-positive individuals, respectively, between the Demographic and Health Survey in 2008 and Egypt Health Issue Survey in 2015.

This gives the impression that the nationwide tremendous efforts to control the HCV epidemic in Egypt were very effective in the reduction of HCV infection particularly in children.

Both HCV seropositive cases were RNA positive. This is understood considering the high specificity of HCV serology and the low frequency of spontaneous clearance of infection.

Liver function tests showed only mild nonspecific rises of alanine aminotransferase and aspartate aminotransferase in a few patients not including HCV-positive cases. This can be explained by the fact that HCV infection is commonly latent for even decades with no clinical nor laboratory signs of liver affection.

Regarding hypoalbuminemia, it is a frequent and early biochemical derangement in critically ill patients with complex etiology. Generally, it is ascribed to diminished synthesis in malnutrition, malabsorption, and hepatic dysfunction or increased losses in nephropathy or protein-losing enteropathy. Inflammatory disorders can accelerate albumin catabolism and reduce its production. Diversion of

synthetic capacity to other proteins (acute-phase reactants) is another likely cause. During critical illness, capillary permeability increases dramatically and alters albumin exchange between intravascular and extravascular compartments [15].

In accordance with most literature, hemophilia A was the most common disorder. Two studies, also on Egyptian children, were done by Abdelrazik *et al.* [16] and by Al Tonbary *et al.* [13]. The first study reported a similar result for hemophilia A but a higher frequency for hemophilia B (14.28%). The second, however, reported a higher frequency for both hemophilia A (61.1%) and hemophilia B (20.8%). On the contrary, Al-Rahal [12] reported that the most prevalent CBD was VWD (42.98%) followed by thrombasthenia (36.71%).

With the exception of hemophilia patients, male-to-female ratio was ~1.0 : 1.5 in our study. This could be related to menstrual bleeding which can lead to the discovery of milder cases in female patients. However, considering the small numbers of cases of each disorder, this observation was not significant ($P > 0.05$).

Frequency of use of each blood product reveals that FFP and PRP are frequently used; despite established diagnosis, as specific products like factor concentrates and platelet concentrates are not readily available in all instances. This is attributable to economic and technical factors that are common in developing countries including Egypt.

Conclusion

In conclusion, the risk of transfusion-associated hepatitis C has declined dramatically in patients with CBD receiving blood products, suggesting effective screening and handling of blood products (including recent use of nucleic acid testing for blood donors).

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Conflicts of interest
There are no conflicts of interest.

References

1 Dorgalaleh A, Fariba RAD. Congenital bleeding disorders. Akbar Dorgalaleh. In. *Congenital Bleeding Disorders*. Cham: Springer; 2018. 27–53.

2 Selvarajah S, Busch M. Transfusion transmission of HCV, a long but successful road map to safety. Antiviral Ther 2012; 17 (7 Pt B):1423–1429.

3 Mohd Hanafiah K, Groeger J, Flaxman A, Wiersma S. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013; 57:1333–1342.

4 Hepatitis C. WHO.Int. 2020. Available at: *https://www.who.int/news-room/fact-sheets/detail/hepatitis-c* [Accessed January 30, 2020].

5 Hajarizadeh B, Grebely J, Dore G. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol 2013; 10:553–562.

6 Denniston M, Klevens R, McQuillan G, Jiles R. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. Hepatology 2012; 55:1652–1661.

7 Pawlotsky JM, Aghemo A, Back D, Dusheiko G, Forns X, Puoti M, *et al.* EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015; 63:199–236.

8 Craxì A, Dusheiko G, Flisiak R. EASL clinical practice guidelines: management of hepatitis C. J Hepatol 2011; 55:245–264.

9 Khuroo MS, Khuroo NS, Khuroo MS. Diagnostic accuracy of point-of-care tests for hepatitis C virus infection: a systematic review and meta-analysis. PLoS One 2015; 10:e0121450.

10 Kucirka L, Sarathy H, Govindan P, Wolf J, Ellison T, Hart L, *et al.* Risk of window period hepatitis-c infection in high infectious risk donors: systematic review and meta-analysis. Am J Transplant 2011; 11:1188–1200.

11 Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017 US Department of Health and Human Services.

12 Al-Rahal N. Inherited bleeding disorders in Iraq and consanguineous marriage. Int J Hematol Oncol Stem Cell Res 2018; 12:273–281.

13 Al Tonbary Y, ElAshry R, El Sayed Zaki M. Descriptive epidemiology of hemophilia and other coagulation disorders in Mansoura, Egypt. Mediterranean J Hematol Infect Dis 2010; 2:e2010025.

14 Kandeel A, Genedy M, El-Refai S, Funk AL, Fontanet A, Talaat M. The prevalence of hepatitis C virus infection in Egypt 2015: implications for future policy on prevention and treatment. Liver Int 2017; 37:45–53.

15 Bansal A, Singhi S, Tiwari L, Jayashree M, Baranwal A. Hypoalbuminemia in critically sick children. Indian J Crit Care Med 2014; 18:565–569.

16 Abdelrazik N, Rashad H, Selim T, Tharwat L. Coagulation disorders and inhibitors of coagulation in children from Mansoura, Egypt. Hematology 2007; 12:309–314.